The development of novel enantiomerically pure ligands for use in the asymmetric catalytic transfer hydrogenation of ketones

Mendonca, Paul

Award date:
2001

Awarding institution:
University of Bath

THE DEVELOPMENT OF NOVEL ENANTIOMERICALLY PURE LIGANDS FOR USE IN THE ASYMMETRIC CATALYTIC TRANSFER HYDROGENATION OF KETONES.

Submitted by Paul Mendonça for the degree of PhD

of the University of Bath

2001

COPYRIGHT

Signed ..Paul C. Mendonca.....

Date ...26th June 2001

ProQuest LLC
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106-1346

ABSTRACT

In this work, the synthesis of novel ligands for use in the transfer hydrogenation of ketones is described. A number of libraries were prepared incorporating hydroxy, imino and amino functionality. These ligands were tested in conjunction with a number of transition metal complexes to identify active catalysts. Optimisation led to the development of a number of highly reactive and selective catalysts, capable of hydrogenating selected ketones in high enantiomeric excesses.

ACKNOWLEDGEMENT

I would like to thank my supervisor Dr. Christopher Frost for his friendship, help and patience over the years. I would also like to thank him and Dr. Piers Gaffney for proof reading this thesis.

I would like to say a big thank-you to Dr. Andrew Weller, Dr. Micheal Willis and Prof. Jonathan Williams for their friendship and advice. Thanks go to Dr. Mary Mahon for running my X-ray crystal structure, Harry and Dave at NMR and John, Ahmed and Russell, our technicians, for their help in finding the odd gem when needed.

I would also like to acknowledge my friends at Johnson Matthey, namely Dr. Barry Murrer, Dr. Christopher Barnard and Dr. Liz Slade, for their support over the last couple of years. Their undying willingness to 'lend' me transition metal complexes (suitably packed in brown envelopes), coupled with their interest in the chemistry and their allowing me to use their facilities were, and always will be, appreciated.

I would like to thank my friends here at Bath Chemistry Department. Perhaps my most lasting memories will be of the many good moments we had during the course of our time together. There are so many people to acknowledge that space does not permit but I must acknowledge at least the following:

Firstly, I would like to thank my research group friends, Kamlesh Chauchan, Christelle Moreau and the fair Catherine Hague for making group gatherings all that more pleasurable. Thanks also go to my good friends Matt Leese, Lawrence Ho, David Holland, Christian Bubert, Parminder Ruprah, Gian

Sohal, Amin Mirza, Virginia Wood, Mike Gill-Carey, Lara, Selma, Christelle Claverie, Jean-Phillipe Cros, Matt Jones, John Swift and the many others.

Finally, I would like to thank my beloved parents and family for their love and support over the ever increasing years of my life.

TABLE OF CONTENTS

ABBREVIATIONS USED

Acac	2,4-Pentadione
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Boc	*tert*-Butoxycarbonyl
cymene	4-Isopropyltoluene
DBA	Dibenzylideneacetone
DCM	Dichloromethane
COD	1,5-Cyclooctadiene
DIOP	2,3-*O*-Isoproylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
DMAP	4-Dimethylaminopyridine
DMPP	Dimenthylphenylphosphine
DMSO	Dimethyl sulfoxide
DPEN	1,2-Diphenylethylene diamine
DPPF	Bisphenylphosphino ferrocene
fac	Facial
MDPP	Menthyldiphenylphosphine
Nbd	Norbornadiene
n.d.	Not determined
NMR	Nuclear magnetic Resonance
(*S*)-(*R*)-Pigiphos	Bis{(*S*)-1-[(*R*)-2-(Diphenylphosphino)ferrocenyl] ethyl}-cyclohexylphosphine
PGM	Platinum group metal

i-PrOH	Isopropanol
Pybox	2,6-Bis(oxazolin-2-yl)pyridine
Pymox	2-(Oxazolin-2-yl)pyridine
S_NAr	Aromatic nucleophilic substitution
trityl	Triphenyl methyl
Ts-DPEN	*N*-(*p*-Toluenesulfonyl)-1,2-diphenylethylene diamine

CHAPTER 1

ASYMMETRIC REDUCTION OF KETONES

1.1 INTRODUCTION

The enantioselective reduction of ketones to furnish non-racemic secondary alcohols continues to be an intensively studied area of research in organic chemistry. This transformation is a key step in the synthesis of many biologically important molecules and synthetic targets which, until relatively recently, was not possible without the use of enzymes. Asymmetric catalytic reduction of carbonyl functions to enantiomerically pure alcohols, without the use of biological systems, is a significant challenge for synthetic organic chemistry.

Over the past three decades much research has been conducted into methods of asymmetric catalysis in search of an efficient and cost-effective method for achieving this aim. Much of the work has involved the use of transition metal complexes for the catalysis. These metals are invariably complexed to a chelating ligand which can act as an activator as well as an asymmetric modifier. This chelating ligand is an enantiopure chiral compound because any chiral induction in the transformation from the prochiral substrate to the enantiomerically enriched product must stem from the effect of the ligand on the catalyst. The chiral ligands used have frequently been derived, *via* a number of steps, from natural products such as amino acids, alkaloids, hydroxy acids and carbohydrates.

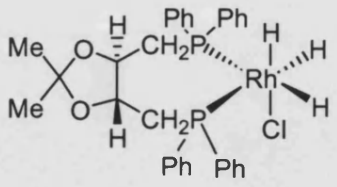
Over the years a number of transformations have been investigated. In this introduction however, the scope will be limited to highlighting some

commonly used methods for the asymmetric reduction of ketones and some key developments in this field.

In particular catalytic hydrogenation, hydrosilylation and transfer hydrogenation will be considered as methods of accomplishing this transformation. The mechanisms of these reactions and some of the more efficient ligands that have been developed for them will be examined.

1.2 ASYMMETRIC HYDROGENATION

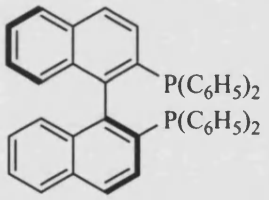
Asymmetric hydrogenation is the transfer of molecular hydrogen to a prochiral substrate molecule resulting in a non-racemic product. This was first carried out in the late 1930's by depositing a metal catalyst on a chiral support and by the 1950's the enantioselectivity achieved using these methods had reached over 60%. This sparked much interest in the subject and in 1972 Kagan revealed the first use of a bisphosphine Rh(III) complex (**1**) for the reduction of α-*N*-acylaminoacrylic acids.[1]



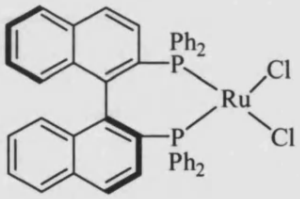
1

Since this early work huge developments have been made in the use of bis-phosphine ligands for transition metal catalysed asymmetric hydrogenation. A vast array of phosphine based ligands have been tested since Kagan's initial results in a bid to optimise the selectivity of the transformation. A number of transition metals have also been employed, such as Rh, Ru and Ir and the reaction has been adopted for the reduction of a number of chemical groups, such as alkenyl (C=C), carbonyl (C=O) and imino (C=N) groups.

Perhaps the single most important bis-phosphine ligand discovered to date for asymmetric hydrogenation is BINAP (**2**), which was developed by Noyori in 1980.[2]



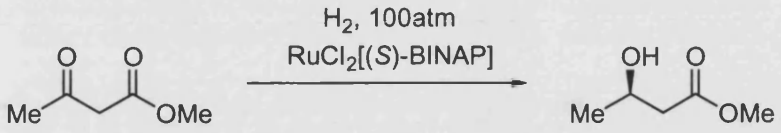
2



3

The ligand has shown itself to be excellent in many asymmetric transformations in conjunction with a range of transition metals. It has also proved an efficient ligand for the ruthenium catalysed hydrogenation of functionalised ketones. The complex **3** has achieved very high selectivities with a wide range of functionalised ketones such as β-keto esters and α-amino ketones. For example, reduction of the β-keto ester (scheme 1.1) using

$RuCl_2$(*R*-BINAP) resulted in near complete conversion (99%) with greater than 99% ee (*R*).[3]

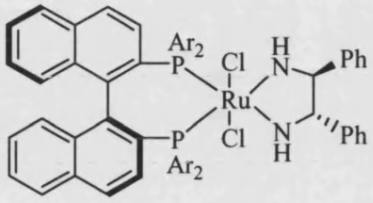


Scheme 1.1 Reduction of a β-keto ester

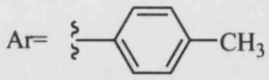
The catalyst **3** was generally very selective and tolerant of a number of functional groups. The main problem was that the catalyst required functionalised ketones (those bearing other functionalities such as hydroxyl or alkoxy groups) and attempts at reducing simple unfunctionalised ketones were generally unsuccessful, leaving little choice but to use other methods for the reduction.

This problem was resolved quite spectacularly by Noyori with the recent introduction of his mixed diamine-bisphosphine-Ru complex [(*S*)(*S*,*S*)-**4**][4] which proved to be very active in the hydrogenation of ketones, even simple unfuctionalised ketones such as acetophenone. The catalyst proved highly active and very selective allowing for very large turnover numbers, with high turnover frequencies, while affording high enantioselectivities. For example, Noyori achieved the conversion of 1-acetonaphthone to the corresponding

alcohol in >99% conversion and 98% ee (*R*) using a catalyst loading of 0.001%.



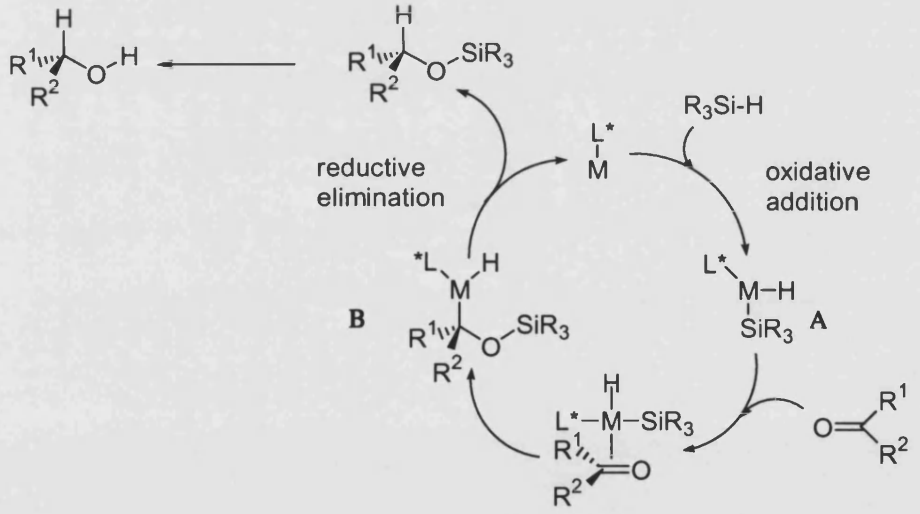
4



The catalyst was however not so selective with acetophenone, giving complete conversion but with an ee of only 80% (*R*). The major flaw inherent in the reaction is the use of hydrogen at relatively high pressures. This requires expensive equipment and adds an element of risk to any industrial usage due to the need to handle hydrogen gas.

1.3 ASYMMETRIC HYDROSILYLATION

The catalytic hydrosilylation of ketones (see scheme 1.2) was first achieved in the early 1970's and has been an active area of research ever since. The reaction involves the oxidative addition of a hydrosilane (R_3Si-H) to a metal catalyst giving a metal hydride complex (**A**). This is followed by insertion of a ketone C=O into the metal-silicon bond to give complex **B**. This metal hydride complex then reductively eliminates to give a silylether, which is subsequently hydrolysed resulting in the formation of the alcohol.

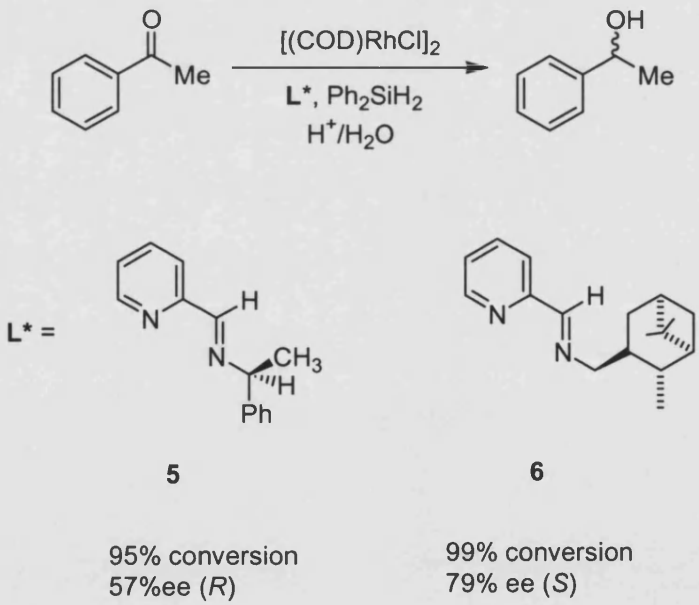


Scheme 1.2 Mechanism of catalytic hydrosilylation

Early work by Ojima found that Wilkinson's catalyst [$RhCl(PPh_3)_3$] was very effective in the hydrosilylation of acetophenone.[5] This finding led to further

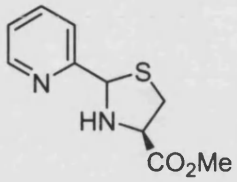
research into the use of chiral Rh(I) catalysts for the reaction. Indeed Rh was to become the metal of choice for much of the research that followed, which initially focussed on the use of phosphine based ligands in conjunction with rhodium (I) complexes. A number of phosphine ligands were used but on the whole these resulted in only moderate enantioselectivities.

In the 1980's, Brunner investigated the use of imine containing ligands for the rhodium catalysed hydrosilylation of ketones.[6] A number of these were prepared and tested in the reaction. These ligands were simple imines formed from the reaction of 2-heteroaryl carboxaldehydes, such as pyridine-2-carboxaldehyde, and enantiopure amines. Some examples are given in scheme 1.3.



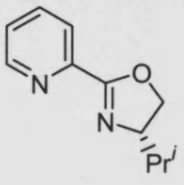
Scheme 1.3

Pyridine was generally the aryl group of choice and the enantioselectivities obtained from ligands **5** and **6** were significant. Higher selectivities were achieved using thiazolidine ligands such as **7** which directed the reduction of acetophenone in conjunction with $[Rh(COD)Cl]_2$ in up to 87% ee (*R*).[7]

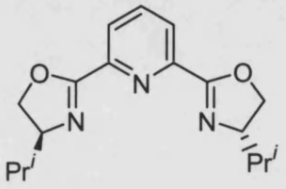


7

In 1986, Brunner published the first use of a new class of ligand, a mono-oxazolinyl pyridine ligand (**8**, Pymox).[8] This ligand type was to revolutionise the choice of ligand for use in enantioselective hydrosilylation. In 1989, Nishiyama published the use of both (*S*)-Pymox (**8**) and a bis-oxazolinyl analogue, (*S*,*S*)-Pybox (**9**). These ligands in conjunction with $[Rh(COD)Cl]_2$ were able to reduce acetophenone in high yield and ee's of 60% and 93% for **8** and **9** respectively. With ligand **9** no activity was observed in the reaction unless an additive such as $AgBF_4$ was added. The additive helps to free co-ordination sites on the metal for substrate binding by removing the chloride ion.



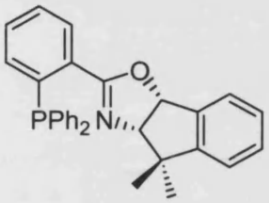
8



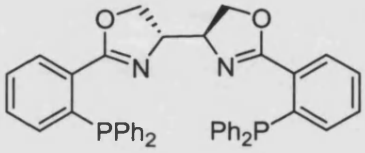
9

More recently, research interest has focussed on the use of diphenylphosphine oxazoline ligands in the reaction. A number of these have been reported and three highly successful ligands are shown below.

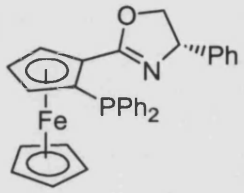
Ligand **10**[9] achieved the reduction of acetophenone in 94% ee (*R*) while **11**[10] achieved the reduction in up to 97% ee (*R*) using $[Rh(COD)Cl]_2$. Hidai obtained (*R*)-1-phenylethanol in up to 95% ee[11] using **12** in conjunction with a ruthenium catalyst $[RuCl_2(PPh_3)_3]$.



10



11



12

Asymmetric hydrosilylation has provided chemists with a route to highly enantioselective reduction of ketones. However, the reaction suffers from the need to use a hydrosilane in stoichiometric quantities, or more commonly a dihydrosilane such as diphenylsilane. These compounds are relatively difficult to handle and are harmful, thus requiring special precautions to be taken in their use and disposal. These factors make hydrosilylation relatively undesirable as an industrial process.

1.4 ASYMMETRIC TRANSFER HYDROGENATION

Catalytic asymmetric transfer hydrogenation involves the reduction of a π-bond by the transfer of hydrogen from a hydrogen donor to an acceptor, the process being promoted by a catalyst. The procedure provides a number of potential advantages to industry for the reduction of ketones based on the ease with which the reaction can be carried out. Generally, using suitable catalysts, the reactions can be carried out at room temperature and at atmospheric pressure, eliminating the need for special industrial equipment and any cost related to heating the reaction. The reaction also uses only relatively harmless reagents, unlike borane reductions, hydrosilylation or hydrogenation and eliminates the expense of handling and disposing of these chemicals.

Having a number of options in terms of which enantioselective reduction method one uses is also an advantage. There is a vast array of potential ketones which could be reduced to give enantiopure secondary alcohols. However, one method (e.g. transfer hydrogenation) may give better results with a particular ketone than another (e.g. hydrogenation). Having so many options when conducting a total synthesis, where the carbonyl reduction may be a key step, is invaluable.

The enantioselective transfer hydrogenation of ketones is a relatively new reaction with the earliest work being published in the early 1980's. During the last 20 years, much progress has been made and the reaction has developed towards an efficient and highly enantioselective process for the reduction of aryl ketones.

This advancement has largely been a result of optimisation of both the metal catalyst used and the enantiopure ligands employed. The best catalysts contained platinum group metals (or PGMs), mainly using iridium, rhodium and ruthenium. A range of ligand types have been successfully utilised in conjunction with these and in this section some of the more notable examples will be highlighted. The ligands can be divided into 3 subsections. These are;

- phosphine containing ligands,
- amine based ligands
- amino alcohol ligands.

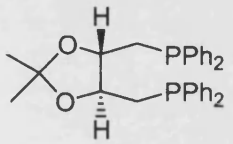
1.4.1 Phosphine containing ligands

A great many phosphine containing ligands have been developed, particularly in the earlier work, when many ligands were brought over from other reactions such as hydrosilylation where they had been successful. These now have been largely superseded by ligands that achieve higher levels of catalyst activation and selectivity.

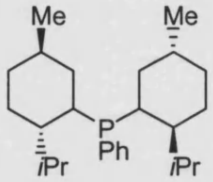
One of the earliest catalysts reported was $H_4Ru_4(CO)_8[(-)\text{-DIOP}]_2$ which had proven effective in the reduction carbon-carbon double bonds by the transfer hydrogenation reaction. However, in the reduction of acetophenone the catalyst only managed to yield 1-phenylethanol in 35% yield and 4% ee.[12]

Later Krause[13] investigated the use of chiral phosphine-iridium complexes in the reduction of ketones. For this purpose, he looked at menthyldiphenylphosphine (MDPP) and dimenthylphenylphosphine (DMPP)

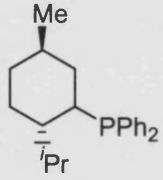
in conjunction with Ir(COD)Acac. Of the 2 ligands, MDPP proved slightly superior in the reduction of acetophenone, providing (*R*)-1-phenylethanol in up to 87% yield with 42% ee. On reducing the reaction temperature from 82°C to room temperature the ee was brought up as high as 48%, however the conversion was reduced to 30%.



(-)-DIOP



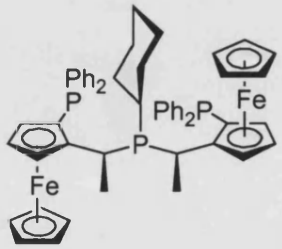
DMPP



MDPP

A number of other generally available chiral phosphine ligands were screened but these generally resulted in low selectivities.

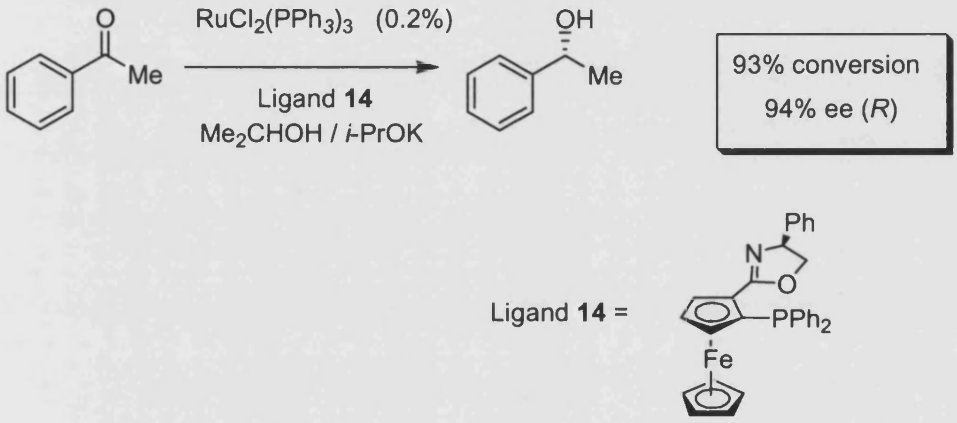
More recently however, phosphine ligands have been developed, capable of higher selectivities. One example was the use of a Ru(II) catalyst complexed to (*S*)-(*R*)-pigiphos (**13**).[14] After some optimisation of the ruthenium catalyst, to obtain {*fac*-[(*S*)-(*R*)-pigiphos]Ru($CH_3CN)_3$}(PF_6), the group managed to produce (*R*)-1-phenylethanol in >99% yield with an ee of 72%.



(*S*)-(*R*)-pigiphos

13

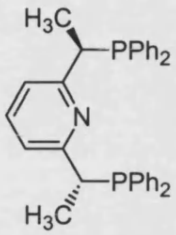
Expanding from phosphine ligands, a number of groups have reported the use of mixed heteroatom ligands containing phosphines. These are commonly mixed P, N ligands and a number of them function as effective catalysts. One such ligand (**14**), developed my Sammakia,[15] delivered superb results producing (*R*)-1-phenylethanol with a conversion of 93% in up to 94% ee (see scheme 1.4).



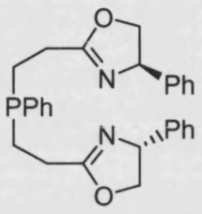
Scheme 1.4

Zhang and co-workers have carried out research into developing mixed P, N ligands for transfer hydrogenation. During the course of their investigations they developed a number of tridentate ligands some of which are shown below. The first of these, (1*R*,1'*R*)-2,6-bis-[1-(diphenylphosphino)ethyl]pyridine (**15**) proved effective in the reduction of acetophenone providing (*R*)-1-phenylethanol in 67% yield with an ee of 48%.[16] This selectivity was improved

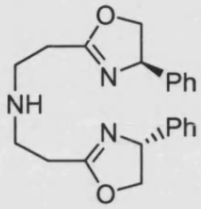
on with ligand **16**, which resulted in a conversion of 72% but with an ee of 79% (*R*).[17]



15



16



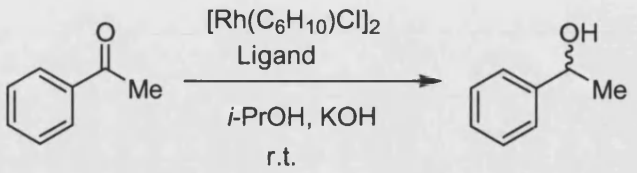
17

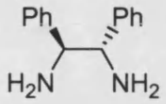
Following on from **16**, Zhang developed a triamine analogue (**17**) which improved the selectivity of the catalyst significantly. Ligand **17**, in conjunction with $RuCl_2(PPh_3)_3$ delivered (*S*)-1-phenylethanol in an excellent 97% ee with 91% conversion.[18]

1.4.2 Amine based ligands

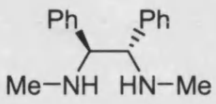
Zhang's triamine ligand (**17**), is only one of many amine-based ligands developed for use in transfer hydrogenation. Diamines have probably been the most commonly investigated ligand class for use in this reaction. A great many have been tested and some excellent ligands have been developed as a result.

Lemaire first looked at chiral C_2-symmetric diamines based around a (1*S*,2*S*)-1,2-diphenylethylene diamine backbone, (DPEN, **18**)[19] and compared it with two ligands (**19** & **20**) derived from **18**. The results are summarised in table 1.1.

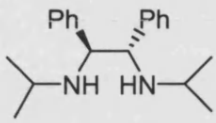




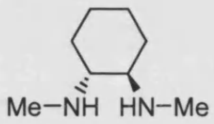
18



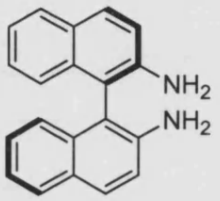
19



20



21



22

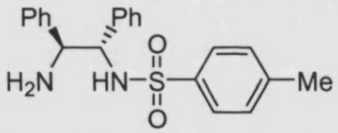
Ligand	% conversion	% ee
18	94	17
19	100	67
20	8	28
21	100	0
22	<1	0

Table 1.1

The most notable point was the increase in enantioselectivity achieved in using the *N*,*N*-dimethyl ligand **19** compared to the both the free diamine (**18**), and to

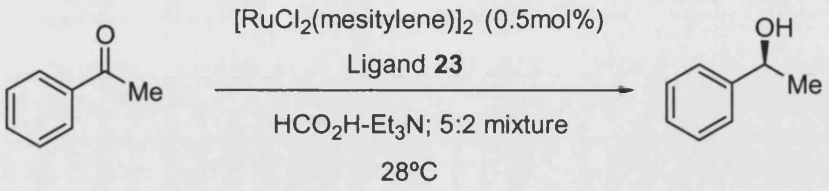
the di-isopropyl substituted diamine (**20**). Lemaire went on to investigate other C_2-symmetric diamine backbones[20]. He found that these ligands (**21** & **22**) gave inferior selectivities to their DPEN analogues. Ligand **21**, though giving complete conversion, gave no enantioselection while ligand **22** showed no activity at all.

Noyori then developed a non-C_2-symmetrical (1*S*,2*S*)-*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylene diamine [(*S*,*S*)-Ts-DPEN, **23**] ligand.[21] In conjunction with $[RuCl_2(mesitylene)]_2$ and KOH in isopropanol this ligand delivered (*S*)-1-phenylethanol in 95% yield and 97% ee, using 0.5 mol% Ru at room temperature.



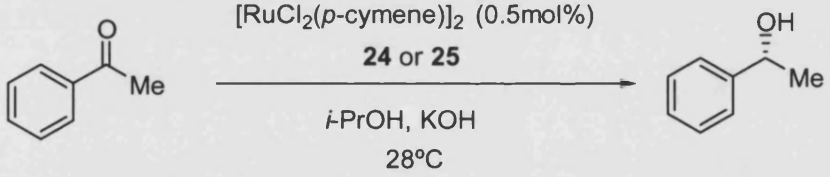
23

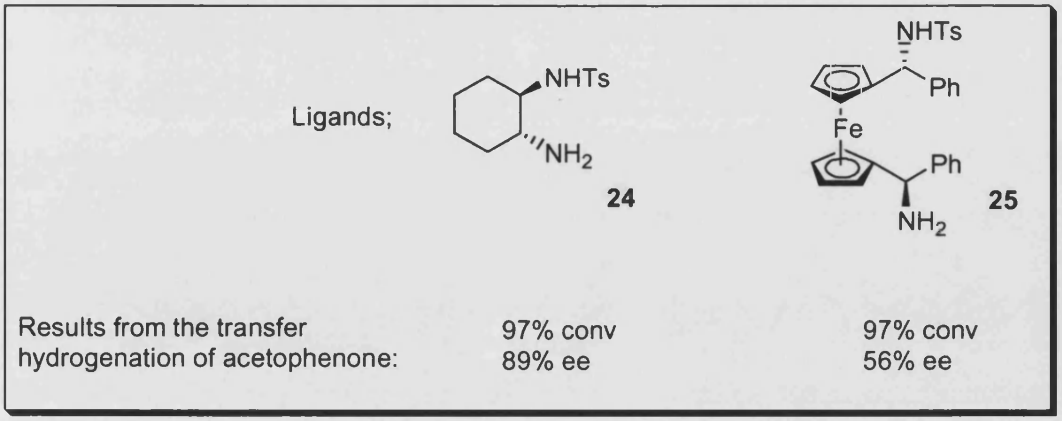
Noyori later found that **23** worked well in alternative transfer hydrogenation conditions using a formic acid-triethylamine (5:2 v/v) mixture.[22] Formic acid can act as a hydrogen donor and, unlike isopropanol, there is no possibility of the back reaction causing loss in enantiopurity. Noyori found that using conditions summarised in scheme 1.5, the ligand could achieve greater than 99% conversion of acetophenone to (*S*)-1-phenylethanol in up to 98% ee. Also, because the possibility of back reaction was eliminated, the substrate could be used in higher concentration.



Scheme 1.5

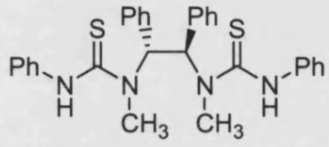
The discovery of the Ts-DPEN ligand encouraged further research into developing mono-*N*-tosyl diamine analogues. Knochel[23] prepared ligands **24** and **25**, to investigate their relative performance compared to Ts-DPEN. He found that they also showed very high activity in the Ru catalysed transfer hydrogenation of ketones. In the reduction of acetophenone these ligands achieved very high conversions at Ru loadings of 0.5 mol% with high ee's. The results are summarised in scheme 1.6.



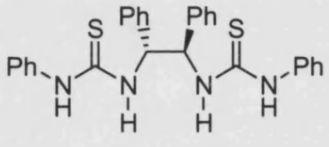


Scheme 1.6

Mono-*N*-tosyl diamines had proved to be very effective in enhancing the activity of Ru(II) based catalysts. However, research into other diamine ligands continued. One example was the development of chiral thioureas as ligands.[24] A number of analogues were prepared and screened including ligands **26** and **27**.

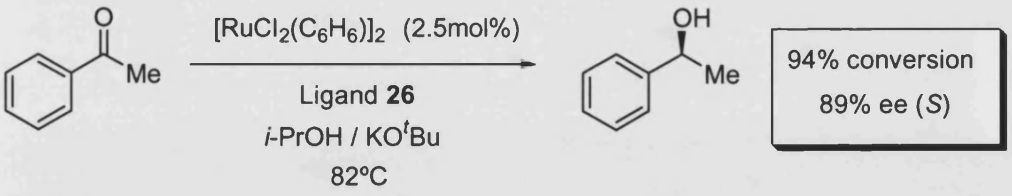


26



27

Ligand **26** produces (*S*)-1-phenylethanol with a conversion of 94% and ee's up to 89%. The methyl groups on the nitrogens of the diamine are vital to achieving high enantioselectivity. If the methyls are replaced by hydrogens as in **27**, the ligand only achieves a 15% conversion to (*R*)-1-phenylethanol with only 24% ee.



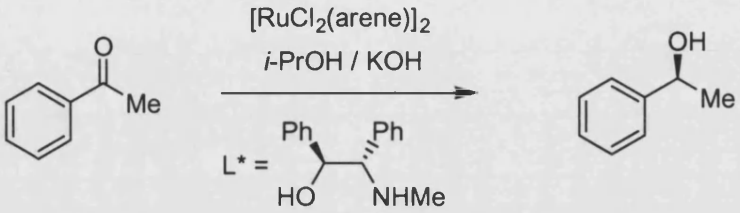
Scheme 1.7

While the results achieved were desirable in themselves, the main advantage of thioureas over many of the ligands that have been developed for use in the transfer hydrogenation, is their ease and low cost of synthesis and their stability

in air by comparison to phosphines. However, the hydrogenation reactions needed elevated reaction temperatures, detracting from any cost advantage they may present.

1.4.3 Amino alcohols in transfer hydrogenation

In 1996, Noyori and co-workers, found that β-amino alcohols were very effective in the transfer hydrogenation of ketones[25]. It was found that simple amino alcohols such as ethanolamine demonstrated a much larger rate enhancing effect on the ruthenium catalysed transfer hydrogenation of ketones than any other ligand type tested to date. In fact the reaction, which achieved turnover frequencies in excess of $220h^{-1}$ using ethanolamine as ligand, was 75 times faster than the reaction without the amino alcohol added. Crucially, it was about 2.5 times faster than mono-*N*-tosylated diamine ligands, such as Noyori's Ts-DPEN ligand (**23**). During the course of the work, Noyori developed (1*S*,2*S*)-*N*-methyl-2-amino-1,2-diphenylethanol (**28**) which proved to be a highly selective ligand for the reduction of acetophenone, in conjunction with $[RuCl_2(C_6Me_6)]_2$ acting as the catalyst precursor. It achieved the reduction of acetophenone to (*S*)-1-phenylethanol in 92% conversion with an ee of 94%. However, the selectivity from this ligand was highly dependant on the nature of the arene ligand on the Ru catalyst, with the ee dropping to 56% when $[RuCl_2(C_6H_6)]_2$ was used instead of the corresponding hexamethyl benzene complex (see table 1.2).

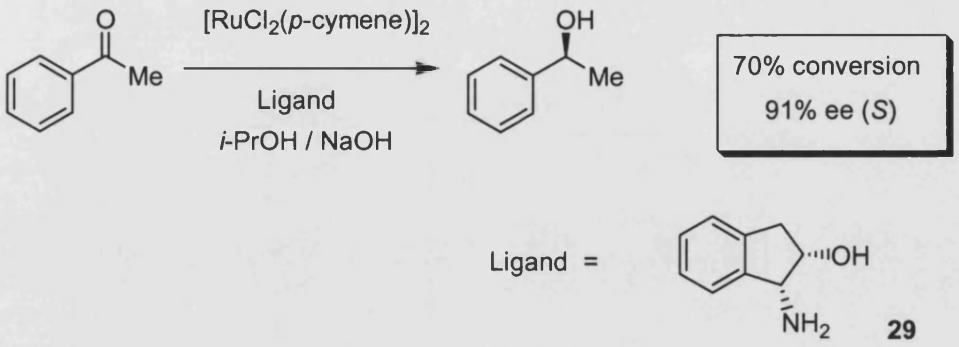


28

arene	% conversion	% ee (config.)
benzene	91	17 (*S*)
p-cymene	97	59 (*S*)
1,3,5-trimethylbenzene	97	56 (*S*)
hexamethylbenzene	94	92 (*S*)

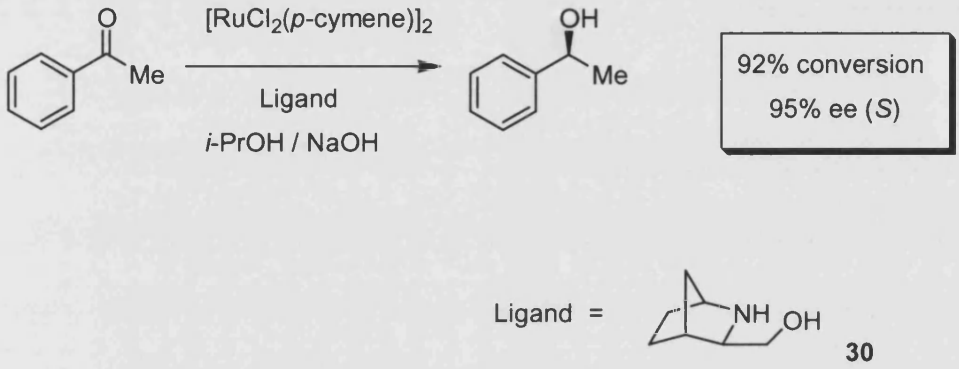
Table 1.2 Results from transfer hydrogenation of acetophenone

Noyori's discovery led to further research into novel amino alcohol ligands for use in transfer hydrogenation reactions. Wills *et al.*[26] found that (1*R*,2*S*)-*cis*-1-amino-2-indanol (**29**) was capable of achieving very high selectivities in the reduction of acetophenone, this catalyst affording (*S*)-1-phenylethanol in 70% yield and 91% ee.



Scheme 1.8

Later, Andersson developed (1*S*,3*R*,4*R*)-2-azanorbornylmethanol (**30**) for use in the Ru catalysed reaction.[27] This ligand was also found to be highly selective, affording (*S*)-1-phenylethanol in 92% yield and 95% ee making it possibly the most selective amino alcohol developed to date.



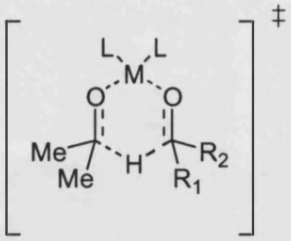
Scheme 1.9

1.4.4 Reaction mechanism

Mechanistically a number of proposals have put forward to explain the reaction. These can be grouped into two categories;

- Direct hydride transfer from a donor molecule to an acceptor
- Transfer of hydrogen via a metal hydride intermediate.

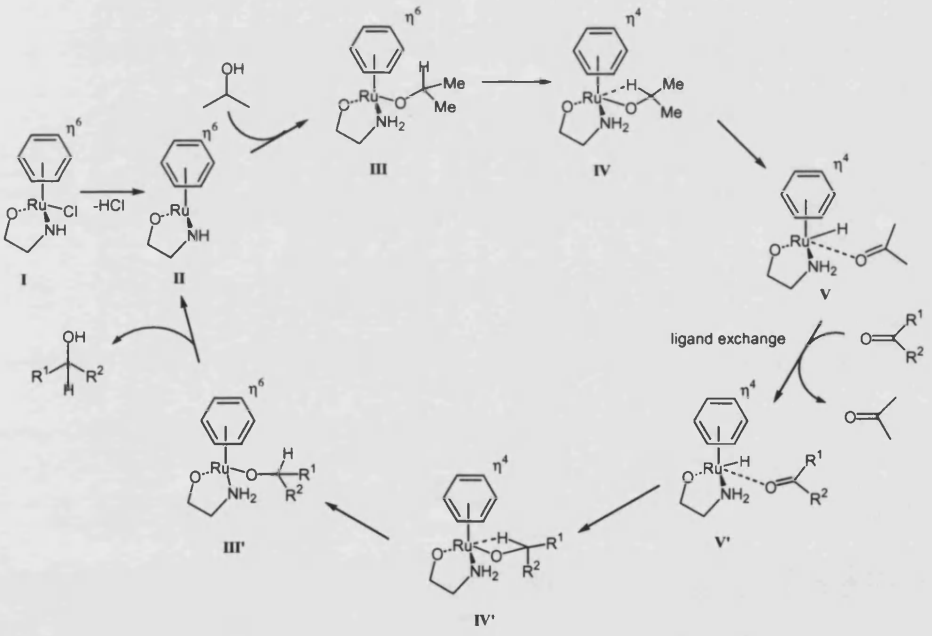
The direct hydrogen transfer mechanism that has been proposed is similar to the Meerwein-Ponndorf-Verley (MPV) reduction which usually involves the formation of a metal alkoxide species. Lemaire[28] has suggested in the past that the mechanism may be similar to this, in that the base used during the transfer hydrogenation reaction deprotonates the isopropanol to form a metal alkoxide species. Those who propose this mechanism suggest that the catalytic intermediate would be a 6-membered transition state **31** (scheme 1.10)



31

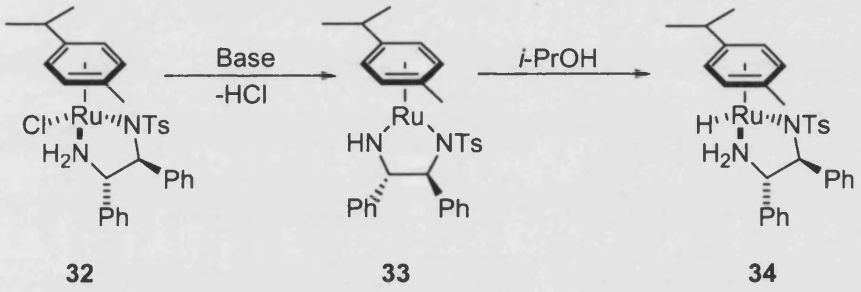
Scheme 1.10 Proposed 6-membered transition state

The reaction then occurs by the direct transfer of the hydride from the carbon of the alcohol (the donor) to that of the ketone (the acceptor). However, this direct hydride transfer mechanism is not supported by substantial experimental evidence. The catalytic intermediate has not been isolated and recent theoretical evidence from molecular modelling calculations has suggested that the reaction proceeds through a metal hydride.[29] The metal hydride mechanism is summarised in scheme 1.11 for a ruthenium-amino alcohol catalyst.



Scheme 1.11 Metal hydride mechanism

This mechanism involves a number of key steps. The first is the base promoted elimination of HCl from the pre-catalyst **I**, to form the 16e⁻ catalytic intermediate **II**. This intermediate is relatively stable, despite being a 16e⁻ species, so that Noyori has managed to isolate a similar diamine Ru complexed intermediate (**33**, scheme 1.12).



32 **33** **34**

Scheme 1.12 Isolated catalytic intermediates

The reason for this observed stability is not fully understood but is believed to stem from substantial back bonding interactions between the lone pairs on the nitrogen and oxygen non-bonding orbitals and the vacant *d*-orbitals of the Ru atom giving rise to substantial double bond character in the Ru-N bond. This theory is further supported by the observation that the length of the Ru-NH bond in **33** is relatively short at 1.897Å, the corresponding bond in **32** is 2.117Å while in **34** it is 2.110Å.[30] Complex **II** can be considered as one of the active catalytic species. It is sufficiently reactive to dehydrogenate isopropanol to give the 18e⁻ Ru hydride species **V** and acetone as a by-product. Again Noyori has isolated an analogue of this species (**34**) and so evidence exists for

its formation. **V'** will then ligate to a ketone to give a complex similar to **IV'**. The hydride is then transferred to the ketone via this cyclic intermediate. Finally loss of the alcohol from **III'** regenerates **II** and the cycle can begin again. Though the mechanism is still largely speculative, there is more evidence to support it than for the direct hydride transfer mechanism.

Recently, however, a new pericyclic mechanism has been proposed by Noyori[31] in which the reaction proceeds through a 6-membered transition state (see figure 1.1). This mechanism, which is believed to be more applicable to diamine and amino alcohol catalysts is discussed more fully in chapter 5.

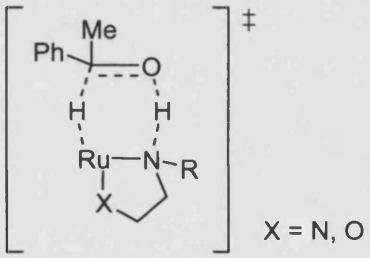


Figure 1.1 Proposed 6-membered transition state

1.5 AIMS OF THE PROJECT

This project is concerned with the development of novel enantiopure ligands for use in the transfer hydrogenation of ketones, in an attempt to improve upon those already available. The need for novel catalysts, and therefore ligands, stems from the belief that no single catalyst can be universally suitable for the reduction of all ketones due to the huge variety of possible ketone substrates. Specifically, it was envisaged that a parallel approach would be adopted for the screening of these novel ligands. A number of small libraries of distinctly different ligand types would be synthesised to verify their activity and enantioselectivity in the transition metal catalysed transfer hydrogenation of ketones. In planning a screening programme some variables were defined at the outset:

- Acetophenone was selected as the test substrate, since it has been extensively studied in other research programmes.
- In carrying out the initial screening of the ligands it was decided to use a relatively high loading of catalyst (5-6 mol%). This was to ensure that a highly selective catalyst would not be missed even if it were only capable of a limited number of turnovers.
- The ligand libraries investigated should offer a fair chance of success in the reaction, but over-analysis of each proposed library was not seen as being consistent with a parallel approach and would only lead to development of ligands similar to those already developed.

- The aim of initial screening was to isolate highly active and selective ligands. Any such hits would then be extended to the preparation of further related analogues to investigate the potential for optimisation. The optimised ligands would then be screened at lower catalyst loadings, and across a range of substrates, to ensure that their selectivity is wider than just to acetophenone.

In developing novel ligands, a number of criteria were thought important:

- The ligand should be relatively simple to prepare, with not more than 2-3 steps needed for its preparation. To prepare a speculative ligand via a large number of steps would be inefficient and incompatible with a parallel approach.
- The ligand must be able to form chelate structures with a metal centre. This is crucial both in terms of obtaining enantioselection and in increasing the activity of the metal complex in the reaction.
- The backbone of any ligand library should be either commercially available or easily accessible and, if possible, relatively cheap.
- The ligand library should allow for a large degree of diversity to be incorporated.
- Both enantiomers of the ligand should be accessible.
- C_2-symmetric or quasi C_2-symmetric ligands would be an advantage.

CHAPTER 2

DEVELOPMENT OF NOVEL DIAMINE LIGANDS

2.1 INTRODUCTION

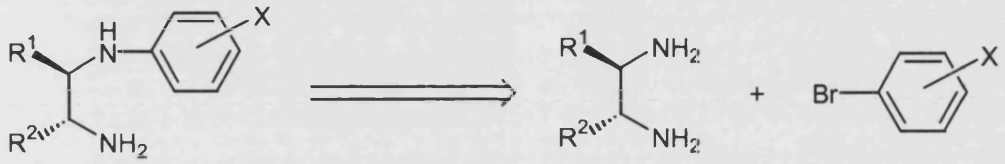
There is a large amount of evidence for the efficacy of diamine ligands in the transfer hydrogenation of ketones, some of which have been highlighted in chapter 1. The most notable of these ligands, and perhaps still the most effective developed to date, is the Ts-DPEN ligand (**23**)[32] developed by Noyori. With this relatively simple and stable mono-*N*-substituted ligand, Noyori achieved high activities and superb enantioselectivities in the Ru catalysed hydride reduction of a range of methyl aryl ketones. Because of this, we wished to investigate a novel range of mono-substituted diamines for use in this reaction.

2.2 A ROUTE TO MONO-ARYLATED DIAMINE LIGANDS

The high activity of Noyori's Ts-DPEN-ruthenium catalyst owed much to the electronic properties conferred on it by the tosyl substituent. Though this has proved to be an effective ligand, derivatives of this type are not trivial to produce in many cases, perhaps explaining why few mono-substituted diamine ligands have been tested. The palladium catalysed amination reaction developed by Hartwig and Buchwald,[33] offered a potential route to a new class of chiral arylated diamines which had not been previously investigated in asymmetric synthesis.

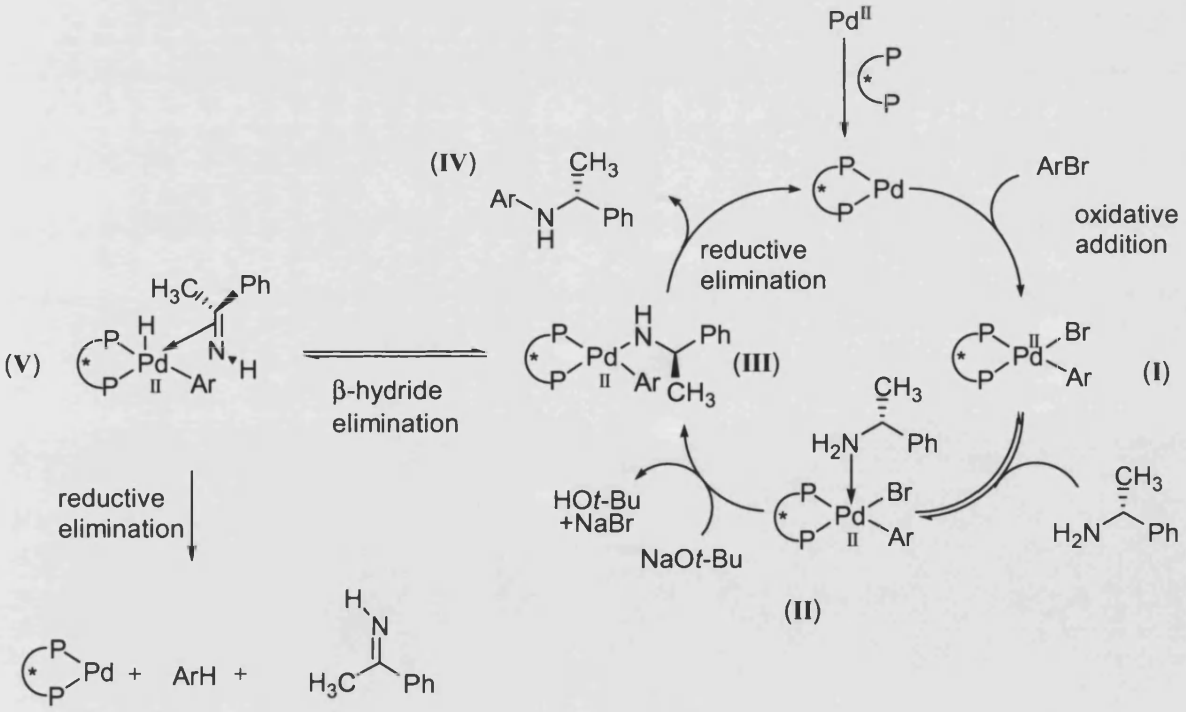
It was hoped that the Pd-catalysed amination reaction could lead to a range of mono-arylated chiral diamine ligands in which the aryl substituent could be varied to induce differences in both the steric and electronic properties of the ligand. These ligands could be obtained in one step from their constituent diamines and aryl bromides (see

scheme 2.1). The large range of aryl substrates available would allow for a high degree of fine tuning, permitting the ligands to be optimised for reactivity and selectivity in the hydride transfer reaction.



Scheme 2.1

From the results of the mechanistic studies carried out by Hartwig and Buchwald, it is thought that the reaction proceeds by the mechanism shown in scheme 2.2.

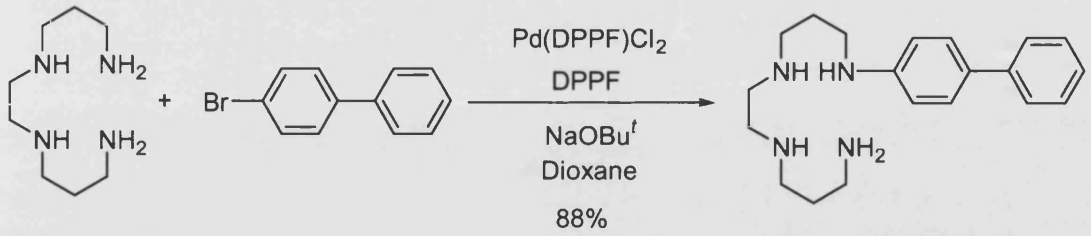


Scheme 2.2 Palladium catalysed amination

The catalytic cycle, using a chelating bis-phosphine ligand, begins with the oxidative addition of the aryl bromide to the Pd(0) species to give **I**, which is then attacked by the amine to give **II**. This is followed by the base promoted removal of HBr from the catalytic species to give the Pd^{II}-amido complex (**III**). Reductive elimination from **III** would furnish the desired *N*-arylated amine (**IV**). It was hoped that the product would not undergo further reaction and that any formation of aryl by-products from the β-hydride elimination of intermediate **III** should be minimised by the use of optimised reaction conditions.

Literature

There was little precedence for the arylation of polyamines, with only the paper by Beletskaya *et al.*[34] in which the arylation of polyamines, including diamines, was investigated. Beletskaya found that polyamines could be mono-arylated in most cases For example, *N,N'*-bis-(3-aminopropyl)-ethylenediamine could be mono-arylated with 4-bromobiphenyl in 88% yield (see scheme 2.3).



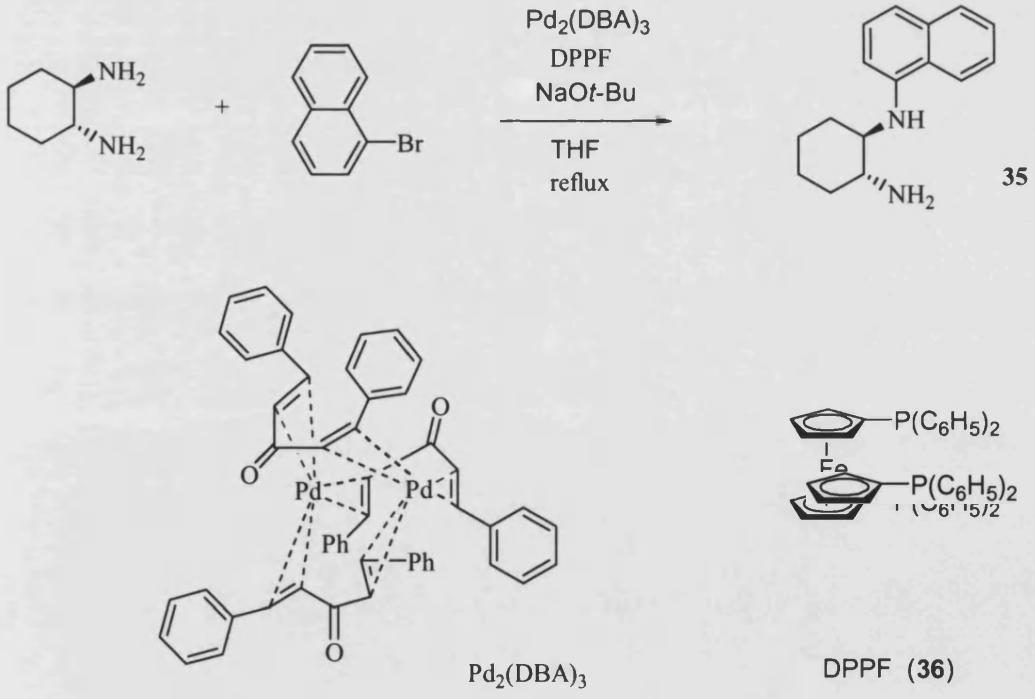
Scheme 2.3

The reaction was substrate dependent, so that *o*-$MeOC_6H_4Br$ and *p*-$MeCOC_6H_4Br$ gave poorer yields (≤20%). With more reactive aryl bromides, such as 1-bromonaphthalene, Beletskaya reported that poly-arylation could occur.

Initial work

To investigate and optimise the mono-arylation of 1,2-diamines, (+/-) 1,2-diaminocyclohexane was predominantly used as the test substrate. Aryl bromides, such as 1-bromonaphthalene, were used because the chromophore has an intense UV absorption which is useful for the efficient characterisation of the products by tlc. A summary of the attempts made to optimise the reaction is given below.

Initial reaction between 1,2-diaminocyclohexane and 1-bromonaphthalene (see scheme 2.4), using our standard conditions similar to previous work on peptidomimetics,[35] gave a low yield of less than 10%, but it was felt that by changing the reaction parameters this could be increased.



Scheme 2.4 Initial test reaction

2.3 OPTIMISATION OF THE REACTION

Changing the loading of diamine used

To ensure that mono-arylation would be favoured, the intention was to use an excess of diamine to aryl bromide, so the effect on the yields of changing the ratio of diamine to the aryl bromide was investigated. This ratio was varied from the initial three equivalents of diamine to aryl bromide to as low as 1.1 equivalents. As can be seen from table 2.1, reducing the loading of 1,2-diaminocyclohexane from three equivalents to 1.4 equivalents resulted in a large increase in isolated yield from 7% to 43%. However, bringing the loading down further to 1.1 equivalents caused the isolated yield to fall off to 30%, indicating that the use of about 1.4 equivalents of diamine was ideal.

Diamine/ArBr ratio	Complex	Ligand	Isolated Yield (%)
3	$Pd_2(DBA)_3$ 2 mol%	DPPF 6 mol%	7
3	$Pd_2(DBA)_3$ 3 mol%	DPPF 9 mol%	13
1.5	$Pd_2(DBA)_3$ 3 mol%	DPPF 9 mol%	41
1.4	$Pd_2(DBA)_3$ 6 mol %	DPPF 18 mol %	41
1.4	$Pd(DBA)_2$ 6 mol%	DPPF 24 mol%	43
1.1	$Pd(DBA)_2$ 6 mol%	DPPF 24 mol%	30

Table 2.1 Effect of diamine to aryl bromide ratio on the isolated yield of 1-*N*-(1-naphthyl)cyclohexane 1,2-diamine (**35**).

The effect of solvent

The effect of solvent was also investigated. Tetrahydrofuran, toluene and *m*-xylene were tested and the results are given in table 2.2. As can be seen there is no noticeable solvent effect, in terms of the reaction yield, with the yield only differing by about 2% in the 3 cases. The solvents were chosen to test for any difference that solvent polarity and higher temperatures would cause. On this basis it was decided to use THF as the solvent of choice, as it gave near identical yields and higher reflux temperatures were seen as unfavourable due to the possibility of racemisation with chiral amines (see below).

ArBr	Diamine	Complex	Ligand	Solvent	% Yield
1 equiv.	1.5 eq.	$Pd_2(DBA)_3$ 3 mol%	DPPF 9 mol%	THF	41
1 equiv.	1.5 eq.	$Pd_2(DBA)_3$ 3 mol%	DPPF 9 mol%	toluene	40
1 equiv.	1.3 eq.	$Pd(DBA)_2$ 6 mol%	DPPF 18 mol%	m-xylene	40

Table 2.2 Effect of changing the solvent on yield of 1-*N*-(1-naphthyl)cyclohexane 1,2-diamine (**35**)

Investigating the effect of catalyst loading on the reaction

Changing the amount of base in the reaction had minimal effect on the yield within the range of 1.2 to 2.5 eq. and so the next parameter investigated was that of the catalyst used. For example doubling the loading of $Pd_2(DBA)_3$ from 3 mol% to 6 mol% resulted in identical yields of 41% (see table 2.3).

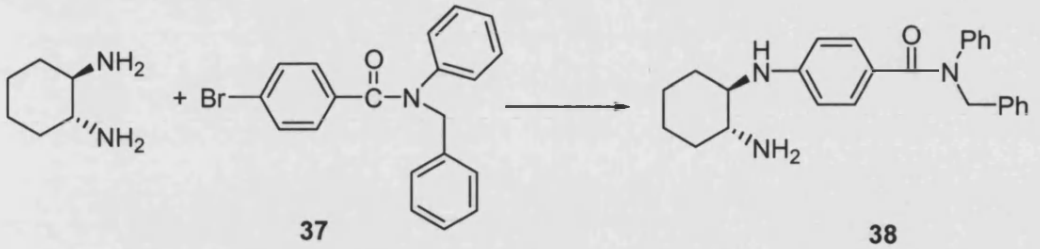
Complex	Ligand	Solvent	% Yield
$Pd_2(DBA)_3$ 3 mol%	DPPF 9 mol%	THF	41
$Pd_2(DBA)_3$ 6 mol%	DPPF 18 mol%	THF	41

Table 2.3 Effect of the catalyst loading on yield of 1-*N*-(1-naphthyl)cyclohexane 1,2-diamine (**35**).

Modification of the catalytic system

The source of Pd was changed from $Pd_2(DBA)_3$ to $Pd(DBA)_2$ and $Pd(DPPF)Cl_2$ and the phosphine ligand changed from DPPF to BINAP and [2,2]phanephos. The changing of ligand should affect the properties of the palladium catalyst, due to the differing steric and electronic properties. The electronic differences, for example, should affect the ease with which the oxidative addition step occurs. Many of the initial reactions had been carried out using $Pd_2(DBA)_3$ and 3 equivalents of DPPF as the ligand. These conditions were known in the literature and had been very efficient in earlier work synthesising peptidomimetics[35]. On trying $Pd(DPPF)Cl_2$ as the Pd source with three equivalents of DPPF the yields were slightly improved over the previous system. For example in the reaction with amide **37**, changing from $Pd_2(DBA)_3$ to $Pd(DPPF)Cl_2$ increased the isolated yield by 10% from 41 to 51%, though in both cases the aryl bromide was completely consumed (see table 2.4). The yields obtained when using $Pd_2(DBA)_3$ and $Pd(DBA)_2$ together with DPPF were

nearly identical in all cases. This was to be expected because they are similar catalysts differing only in the level of aggregation. Therefore, the $Pd(DPPF)Cl_2$ /DPPF catalyst proved slightly superior to the same ligand being used with $Pd_2(DBA)_3$ or $Pd(DBA)_2$.



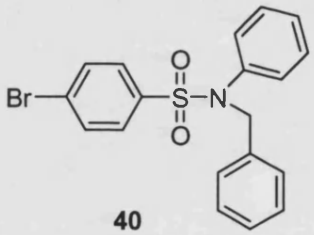
37 38

Complex (loading)	Ligand (loading)	Isolated yield (%)
$Pd_2(DBA)_3$ 5 mol %	DPPF 15 mol%	41
$Pd(DPPF)Cl_2$ 8 mol %	DPPF 15 mol%	51

Used diamine: ArBr ratio of 1.5:1

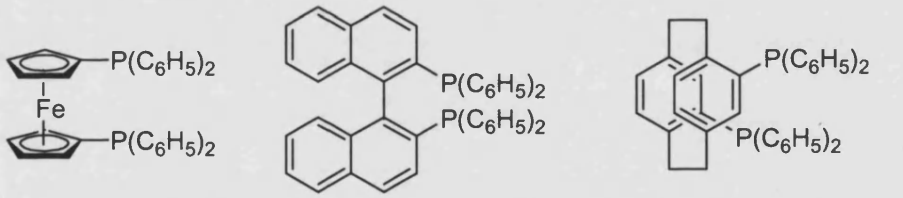
Table 2.4 Comparison of catalysts

It was becoming clear that the problem was not solely confined to a lack of complete reaction because in the majority of reactions, the aryl bromide substrates were completely consumed. This was particularly the case, with sulphonamide **40**, amide **37** and also, in some cases, 1-bromonaphthalene where the aryl bromides were fully consumed within a few hours but the isolated yields were only moderate and arene by-products could be observed in most cases by tlc.



40

It was hoped that by further changing the nature of the catalytic system the problems of side products and occasionally incomplete reactions could be resolved. The next parameter to be changed was the ligand. Other investigators have shown that a number of phosphine ligands can be used in the reaction.[36] However, in choosing the ligands it was decided that it should be confined to readily available bis-phosphine ligands. The use of bidentate ligands rather than mono-phosphines, which had been shown to be active in the amination reaction,[37] was necessary to reduce the likelihood of racemisation of the chiral amine due to possible β-hydride elimination from a catalytic intermediate (see section 2.3).[38] To this end, three different bis-phosphine ligands (scheme 2.5) were investigated.



DPPF (**36**) (+/-)-BINAP (**2**) (+/-)-[2.2]phanephos (**39**)

Scheme 2.5 Structures of phosphine ligands used

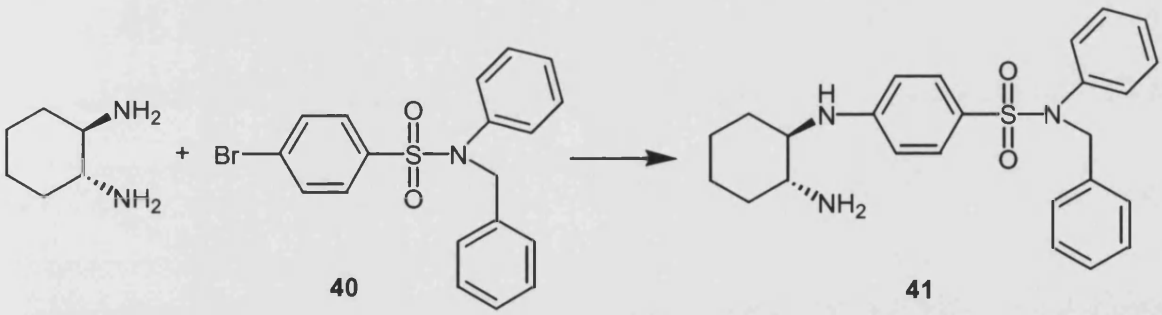
BINAP was examined because it was known to be effective in the reaction. Also it is believed that the formation of the Pd-BINAP complex is more energetically favourable than Pd-DPPF due to the smaller bite angle of BINAP. This leads to a more tightly bonded complex and should therefore reduce any potential poisoning of the catalyst by the diamine. Changing from DPPF to BINAP as ligand gave a noticeable increase in yield in the test reaction (see table 2.5).

Complex (6 mol %)	Ligand (loading)	Isolated yield (%)
$Pd_2(DBA)_3$	DPPF 18 mol%	41
$Pd(DBA)_2$	BINAP 12 mol%	50
$Pd(DBA)_2$	[2,2]Phanephos 18 mol%	0

Ratio of 1-bromonaphthalene/diaminocyclohexane; 1:1.4

Table 2.5 Effect of changing ligand on reaction yields

Noting that the $Pd(DPPF)Cl_2$/DPPF system was superior to $Pd_2(DBA)_3$/DPPF it was then compared to $Pd(DBA)_2$/BINAP in the synthesis of **41**. As can be seen a significant yield increase was observed from 52% to 70% at a 6 mol% loading of Pd (table 2.6).



40 **41**

Complex (6 mol %)	Ligand (loading)	% Yield
$Pd(DPPF)Cl_2$	DPPF 18 mol%	52
$Pd(DBA)_2$	BINAP 12 mol%	70

Table 2.6 Preparation of **41**

Attempted use of [2,2]phanephos (**39**), a novel bisphosphine ligand[39] developed by *Merck*, in the test reaction failed to give any detectable product, highlighting the importance of careful selection of the bis-phosphine ligand. The observation that BINAP was superior to DPPF as the ligand suggested that the problems may have stemmed in part from a potential competitive effect between the diamine and the bis-phosphine for complexation to palladium. In the event of ligand competition the Pd catalyst would effectively be poisoned and this could explain the failure of the reaction in some cases to go to completion. Interestingly, when attempting the reaction using 3 equivalents of diaminocyclohexane to 1-bromonaphthalene and BINAP as the ligand, the isolated yield is roughly equivalent (*ca.* 50%) to that achieved in the previously optimised conditions when using only 1.5 equivalents of ArBr (see table 2.1). This suggests that the reaction is more tolerant of excess diamine with BINAP than when using DPPF. However, the differences in observed yields from using different catalytic systems most probably lies in variable levels of side reactions. During the course of this work the bis-phosphine ligand was always added in excess to the palladium. The extent of this loading seemed to have no noticeable effect on the yield within the ranges used in the experiments (1.5 to 4 equivalents of bis-phosphine to Pd).

Attempts at using Cs_2CO_3 as the base instead of NaO*t*-Bu did not lead to higher yields and the use of $Pd(OAc)_2$ as the catalyst precursor together with BINAP proved inferior to using $Pd(DBA)_2$.

Use of other additives

The use of additives such as 18-crown-6 and LiCl failed to improve the reaction yields. In fact very poor yields were observed in both cases. The use of 18-crown-6 would be expected to have an activating effect on the base - presumably why Buchwald has reported room temperature amination reactions using this as an activator.[40] However, addition of crown ether to the arylation of 1,2-diaminocyclohexane at 60°C gave a very low yield of 8%.

It is known that the addition of lithium chloride can improve the reactivity and yield in the palladium catalysed Heck reaction[41]. However, the reaction using LiCl resulted in a yield of only 11%.

Reactions were typically allowed to reflux over a period of about 16-24 hours, or less if the reaction was complete. It was thought that this time period should suffice, especially considering the relatively high loadings of palladium used. In some cases, particularly when using 1-bromonaphthalene or 4-bromobiphenyl, the aryl bromide was not completely consumed, but elongating the reaction time to several days usually resulted in slightly lower yields.

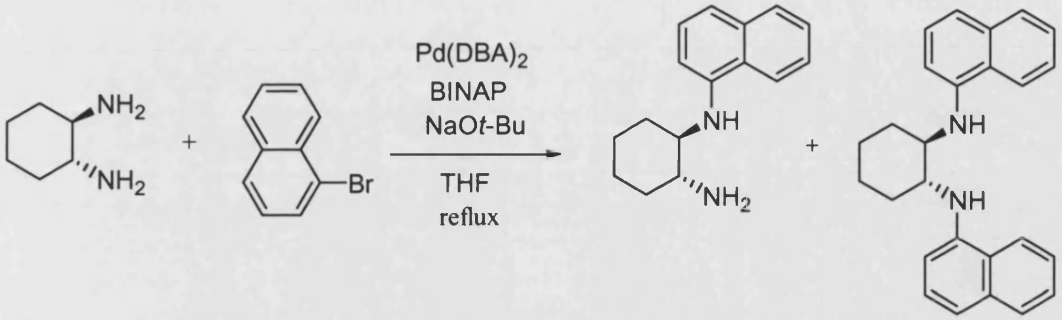
Changing conditions had only provided limited success in attaining higher yields of the desired products. Tlc analyses of these reactions showed that starting material remained in some cases, but in most cases other arene side products were visible. It was originally thought that the side products formed were a result of the reduction of the aryl bromide, to give the corresponding arene. Some evidence for this came from GC studies of the reactions of 1-bromonaphthalene and 4-bromobiphenyl which showed the formation of a peak of similar retention time to that of the respective arene. However, the levels of this product were quite small and fluctuated somewhat

over time, suggesting that the peak could also have been derived from a reaction intermediate. Throughout the work it had been thought that the bis-arylated products were not being formed, due to the use of excess diamine to aryl bromide and the findings of other work carried out within the group. It was therefore assumed that any side products were probably the result of reduction of the aryl bromide or other side reactions. However, NMR analysis of the reactions of 1-bromonaphthalene and isolation of the arene by-product showed that the main by-product was bis-arylated diamine. These products were of very similar R_f to the arene starting material but stained with vanillin.

In the reaction with diaminocyclohexane (1.4 equivalents used to 1-bromonaphthalene) the ratio of mono-arylated diamine (**35**) to bis-arylated diamine (**42**) was approximately 2:1 from the ^{1}H-nmr of the crude reaction (see scheme 2.6). The bis-arylated product (**42**) had a characteristic doublet at 6.80ppm and a multiplet at 3.63ppm, each peak corresponding to two protons while the corresponding peaks in the mono-arylated diamine (**35**) came in at 6.72ppm and 3.20ppm respectively, each integrating for one proton.

A similar observation was made in the reaction of bromonaphthalene with DPEN (see scheme 2.7). Here too there was a significant amount of the bis-arylated product (**44**) but this time the proportion of mono-arylated product (**43**) was higher at about 80% after a period of 4 hours.

The formation of the bis-arylated products in these quantities explains the moderate yields of the desired mono-aryl products. Though the reactions in some cases did not lead to complete consumption of the aryl bromide, the main problem appeared to be formation of the bis-arylated diamines, the exact balance depending on the substrates.

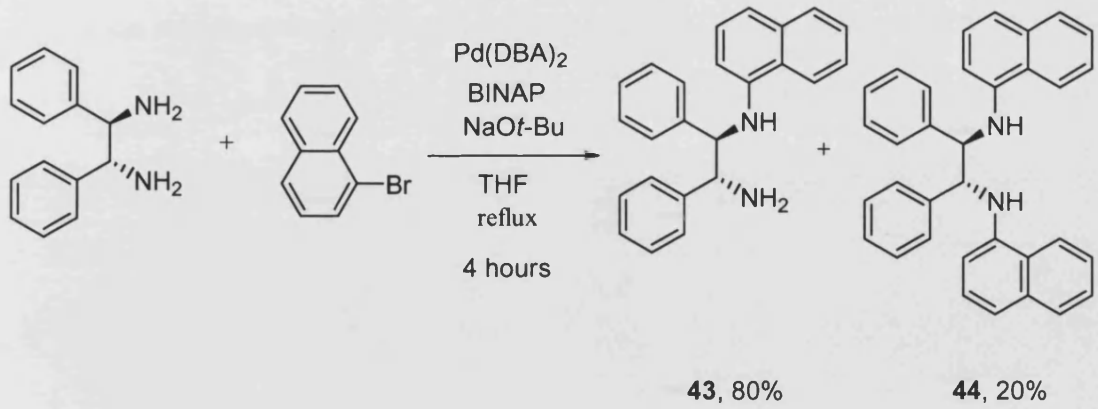


35 **42**

Reaction time	% **35**	% **42**
24 hrs	64	36
48 hrs	58	42

Table 2.7 Ratio of aryl diamine products

Scheme 2.6

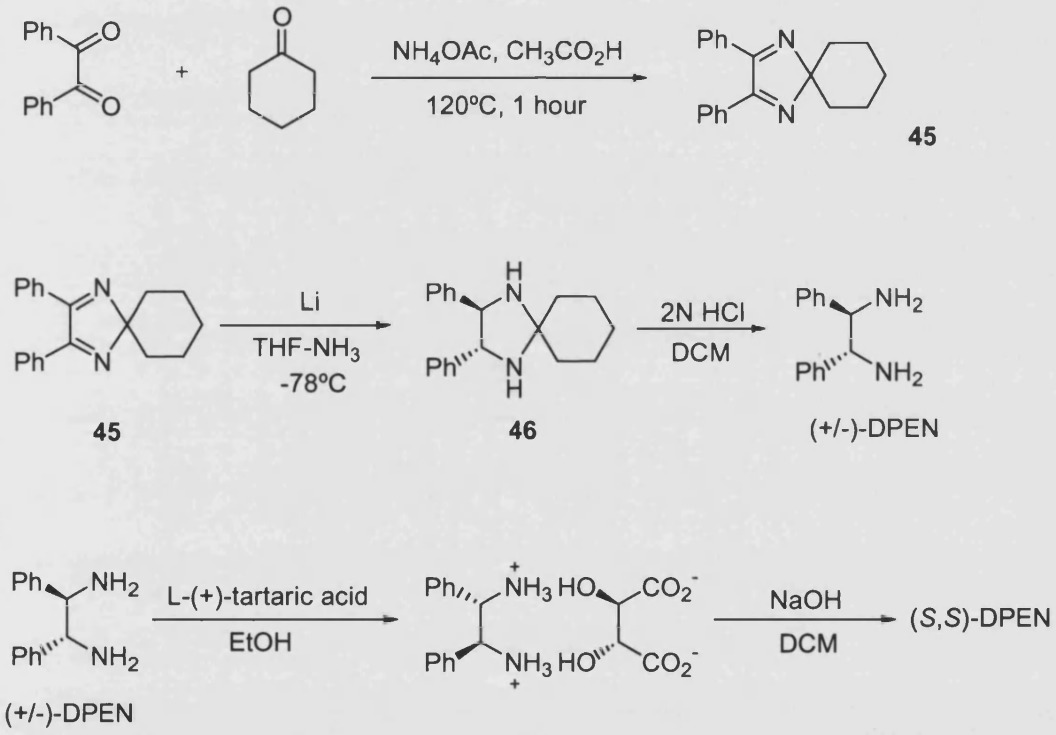


43, 80% **44**, 20%

Scheme 2.7

In conclusion, some success was achieved in bringing the initially very low yields up to at least moderate and, in some cases high yields. While the reaction could benefit from further optimisation, it was felt that for the purposes of this project the current results were sufficient.

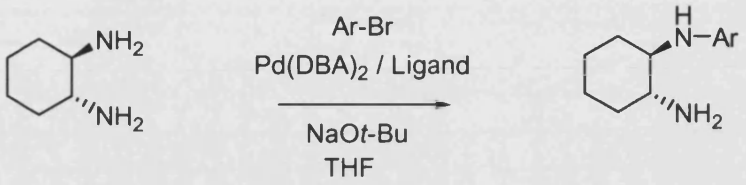
Due to the high cost of (1*S*,2*S*)-DPEN, this was prepared following the procedure of Corey[42] (scheme 2.8).



Scheme 2.8

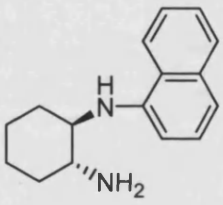
A number of analogues of both (1*R*,2*R*)-diaminocyclohexane and (1*S*,2*S*)-DPEN were prepared and their structures are given in schemes 2.9-2.10. The yields obtained show pronounced substrate effects dependent on both the nature of the aryl bromide

and of the diamine. So, for example, DPEN proved the better diamine substrate, resulting in higher yields of the desired product in most cases. This effect is almost certainly due to a lower level of the bis-arylated by-product formed with this substrate.



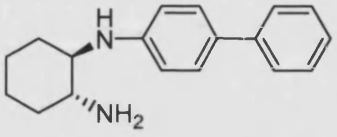
Ligands prepared from (1*R*,2*R*)(-)-1,2-diaminocyclohexane

35



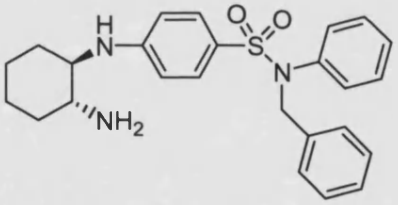
50%

47



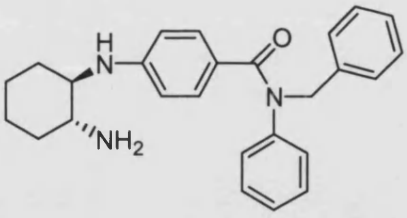
52%

41



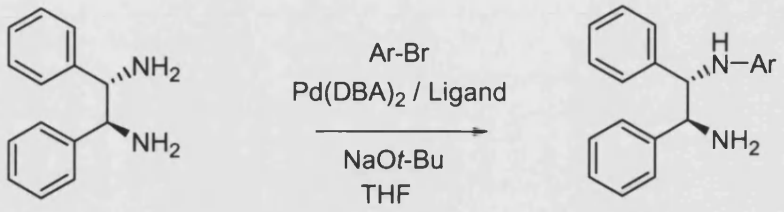
70%

38



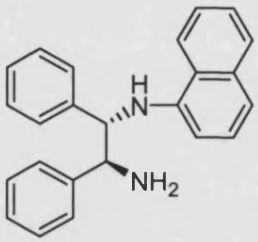
51%

Scheme 2.9



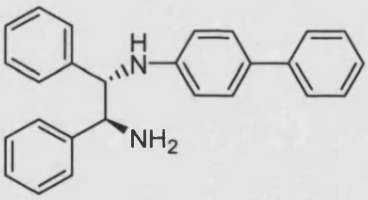
Ligands prepared from (1*S*,2*S*)(-)-1,2-diphenyl-1,2-ethanediamine

48



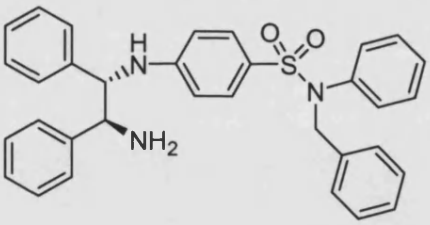
62%

49



40%

50

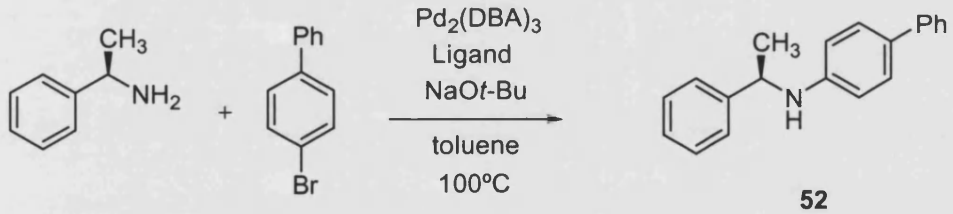


84%

Scheme 2.10

2.3 INVESTIGATION OF CHIRAL INTEGRITY

For the reaction to be useful in preparing enantiopure diamine ligands, it was essential that it proceeded without any significant deterioration of the enantiomeric purity of the diamine. Buchwald *et al.*[43] examined palladium catalysed arylation of a number of optically active amines in which they investigated the effect that different catalytic systems have on levels of racemisation. In a test case, the reaction between (*R*)-α-methylbenzylamine and 4-bromobiphenyl (table 2.9), he found that when using $Pd_2(DBA)_3$ in conjunction with either BINAP or DPPF no significant loss in enantiomeric purity was observed. However, when using P(*o*-tolyl)$_3$ as the ligand the enantiopurity of the amine fell dramatically.



52

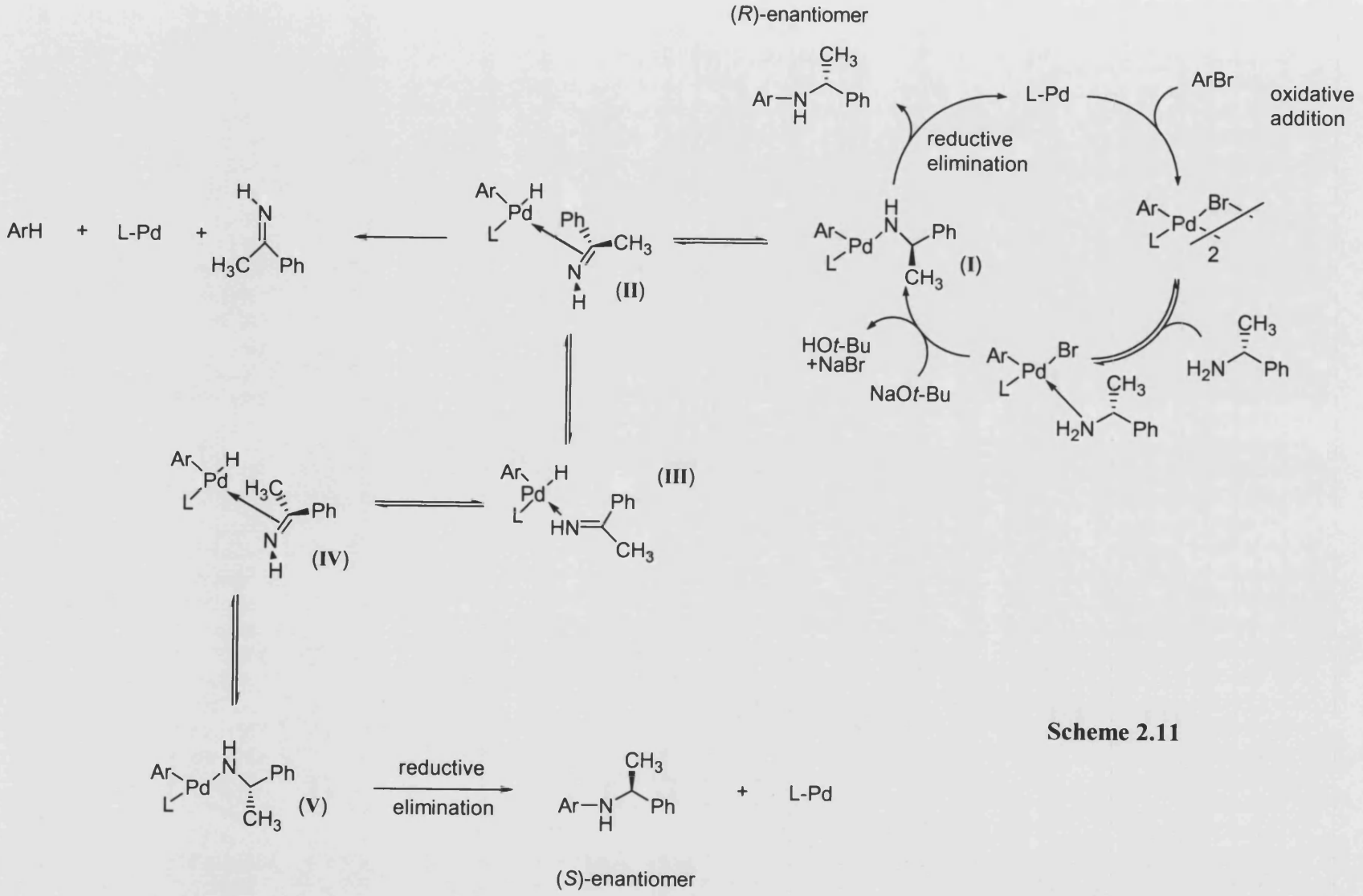
Ligand	% ee of 52
DPPF	>99
BINAP	>99
P(o-tolyl)$_3$	70

Table 2.9

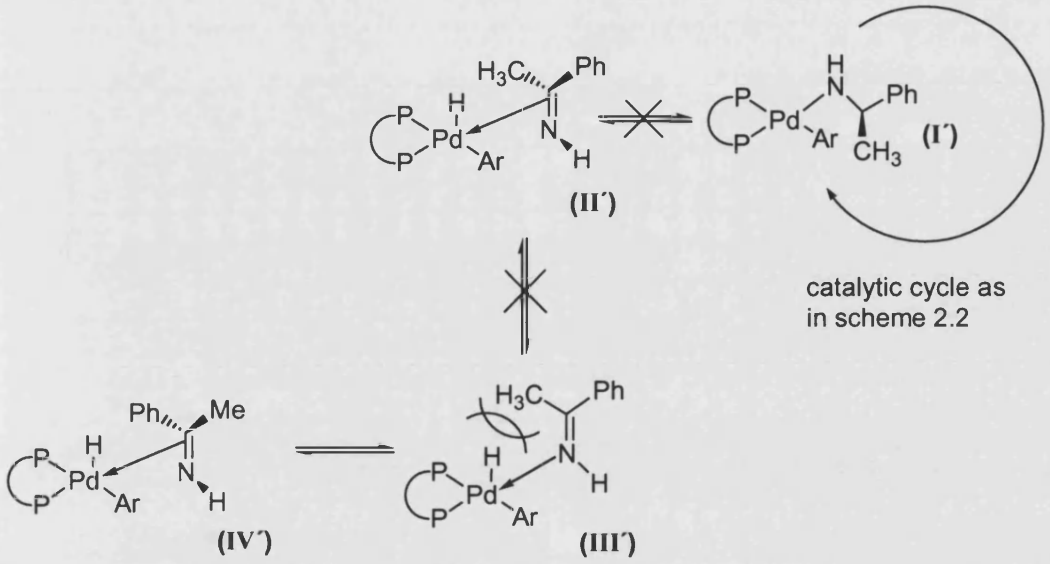
He found that racemisation also occurred when using other monodentate phosphine ligands such as P(1-naphthyl)$_3$ and P(*o*-methoxyphenyl)$_3$. The extent of racemisation with P(*o*-tolyl)$_3$ was little affected by the ratio of phosphine to Pd but as the reaction temperature was increased the extent of racemisation increased. The use of bidentate ligands was crucial in maintaining the enantiomeric purity of the amine during the reaction. Through further probing of the mechanism, Buchwald suggested a reason for this observed effect (see scheme 2.11).

It is thought that the racemisation that occurs with monophosphine ligands is a direct result of the formation of the two Pd^{II}-amino complexes **I** and **V**. Reductive elimination of **I** results in the desired arylated amine. However, β-hydride elimination, a potentially competitive and reversible reaction, initially leads to a π-coordinated Pd^{II}-imino complex (**II**). This can undergo reductive elimination to give an imine and the hydrodehalogenated arene (ArH).

Buchwald suggested that **II** could also interchange from the π-coordinated complex (**II**) to the σ-coordinated Pd^{II}-imino complex (**III**). Due to relatively low barriers to rotation, this in turn could return to the enantiomeric π-complex (**IV**), which is π-coordinated on the opposite prochiral face of the imine to that of complex **II**. Complex **IV** could go on to form the σ-bonded complex (**V**), and reductive elimination of this complex would result in the opposite enantiomer of the arylamine product and hence cause racemisation.


(R)-enantiomer
ArH + L-Pd +
(II)
(I)
reductive elimination
L-Pd
ArBr
oxidative addition
HOt-Bu +NaBr
NaOt-Bu
(III)
(IV)
(V)
reductive elimination
+ L-Pd
(S)-enantiomer

Scheme 2.11

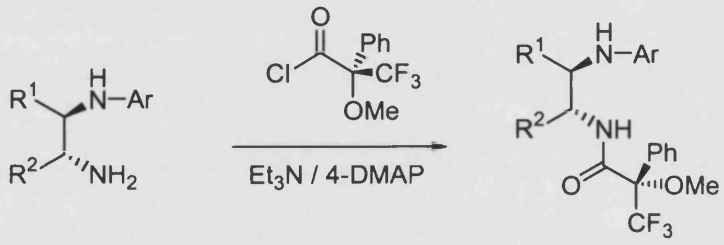


Scheme 2.12

The use of a bis-phosphine ligand probably prevents the β-hydride elimination of of **I′** thus not allowing the formation of **II′** and so preventing any racemisation. It is believed that with bis-phosphine ligands both phosphorus atoms stay bonded to the palladium throughout the catalytic cycle. The square planar Pd complex **I′** is therefore 4-coordinate, unlike with monophosphine ligands where a phosphine can fall off the metal forming a 3-coordinate species. This 4-coordinate species makes β-hydride elimination unfavourable due to the lack of a suitable empty d-orbital for the β-hydride to attack.

Buchwald has also argued that even if **II′** were to form, formation of the σ-coordinated intermediate **III′** would be unfavourable due to steric interactions between the methyl group of the imine and the bulky metal centre (see scheme 2.12).

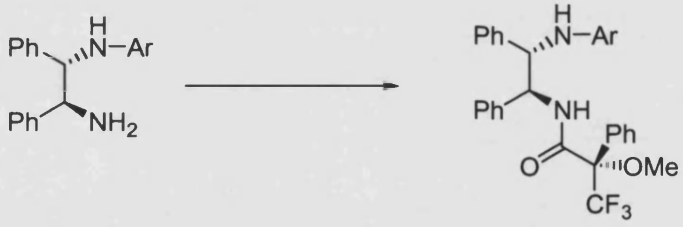
It was necessary to check the enantiopurity of the prepared mono-aryl diamine ligands. However, attempts at using chiral HPLC proved unsuccessful and so Mosher's amides were formed from the diamines by reacting them with enantiomerically pure (*R*)-MTPA-Cl (scheme 2.13). The enantiomeric excesses of the amines were derived from the diasteromeric excesses of the amides observed by ^{19}F-NMR.



Scheme 2.13 Synthesis of MTPA-amides

All the amides investigated were diastereomerically pure (>97% de) with only one significant ^{19}F-NMR peak corresponding to the amide observed. The ^{1}H-NMR spectra also indicated only one diastereomer was present. Scheme 2.13 lists the amides formed together with their resonance frequency in the ^{19}F-nmr ($CDCl_3$) in ppm.

Compound no	Ar	^{19}F-nmr signal
53	1-$C_{10}H_7$	-69.47
54	*p*-Ph-C_6H_4-	-69.21
55	*p*-($C_6H_5CH_2N(C_6H_5)SO_2)C_6H_4$-	-69.34



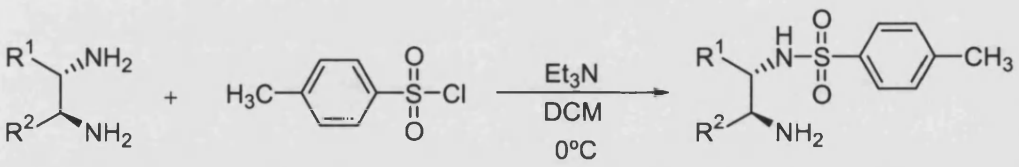
Compound no.	Ar	^{19}F-nmr signal
56	1-$C_{10}H_7$	-68.88
57	*p*-Ph-C_6H_4-	-68.99
58	*p*-($C_6H_5CH_2N(C_6H_5)SO_2)C_6H_4$-	-69.20

Scheme 2.13 Amides prepared

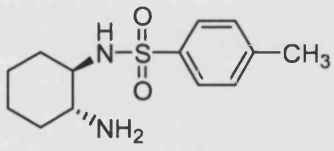
To check that ^{19}F-nmr was suitable for distinguishing between these diastereomers, a number of Mosher's amides were prepared from racemic modifications of the aryl diamines. In each case, these showed 2 peaks, of equal intensity, each corresponding to one diastereomer. So for example, **53** prepared from *rac*-**35** showed peaks corresponding to the diastereomers at –69.11 and –69.47 ppm and **56** (prepared from *rac*-**48**) at –68.90 and –69.26 ppm. The fact that the diastereomeric amides could be distinguished by ^{19}F-nmr indicated that this was a suitable method for checking enantiomeric purity of the diamines. A more definitive picture would have been obtained if amides from *cis*-diamine analogues had been prepared, as this would have given ^{19}F-nmr peaks for all the possible diastereomers. However, the data obtained was relatively conclusive, showing that no noticeable racemisation had occurred.

2.4 RESULTS FROM TRANSFER HYDROGENATION

The ligands were tested in the ruthenium catalysed transfer hydrogenation of acetophenone, summarised in table 2.10. The results were quite disappointing, with all ligands giving significantly lower ee's than either TsDPEN (**23**) or TsCYDN (**51**), which were prepared as shown in scheme 2.14.

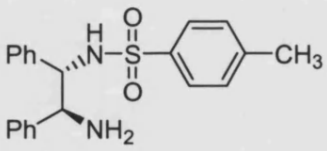


Ligands;



(*R*,*R*)-TsCYDN, **51**

Yield=41%



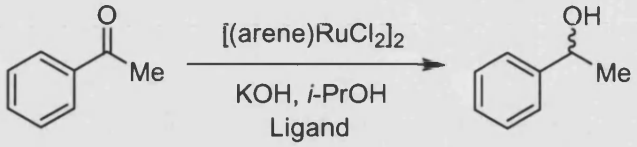
(*S*,*S*)-TsDPEN, **23**

Yield=60%

Scheme 2.14

The most effective of the novel ligands tested, *p*-sulfonamide **50**, resulted in (*S*)-1-phenyl ethanol in a relatively high ee of 60% at 40°C with [Ru(*p*-cymene)Cl_2]$_2$. While this is a fair level of selectivity, ligand **51** resulted in an ee of 77% at 40°C. The selectivity of **50** in conjunction with [Ru(C_6H_6)Cl_2]$_2$ was significantly lower at 43%. This variation in selectivity with the change of

arene has already been noted in literature. In general, the rates of the reactions with the ligands developed here were relatively slow, and in some cases, activity was very low with the reactions giving poor conversions even at these relatively high catalyst loadings (5-6mol%).



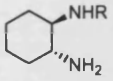
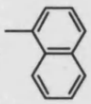
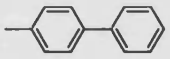
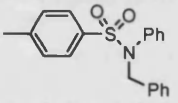
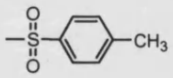
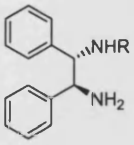
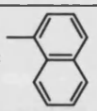
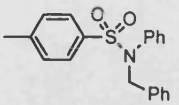
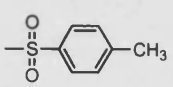
	Ligand		Metal	Temp / time	% Conv	% ee
	R= 	**35**	[Ru(*p*-cymene)Cl_2]$_2$	80°C 21 hrs	<5	n.d.
	R= 	**47**	[Ru(*p*-cymene)Cl_2]$_2$	80°C 2 hrs	<10	4 (*R*)
	R= 	**41**	[Ru(*p*-cymene)Cl_2]$_2$	40°C 18 hrs	31	6 (*R*)
	R= 	**51**	[Ru(*p*-cymene)Cl_2]$_2$	40°C 1.5 hrs	58	77 (*R*)
			[Ru(*p*-cymene)Cl_2]$_2$	0°C 18 hrs	31	94 (*R*)
	R= 	**48**	[Ru(C_6H_6)Cl_2]$_2$	40-45°C 5 days	66	21 (*S*)
	R= 	**50**	[Ru(*p*-cymene)Cl_2]$_2$	40°C 11.5 hrs	95	60 (*S*)
			[Ru(C_6H_6)Cl_2]$_2$	40°C 14 hrs	>95	43 (*S*)
	R= 	**23**	[Ru(*p*-cymene)Cl_2]$_2$	0°C 14 hrs	93	96 (*S*)

Table 2.10 Results from transfer hydrogenation of acetophenone

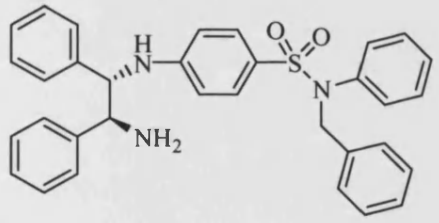
The results also showed that the sulfonated *N*-aryl ligands (**41** & **50**) were more active than the other analogues tested, possibly due to the electronic properties of the substituent. There is precedence for this effect in, for example, the comparison of ligands **23** and Me-DPEN **59** (see section 3.1). Noyori found that the selectivity of both ligands were similar in the transfer hydrogenation of ketones. However, he suggested that the higher activity of the sulfonamide ligand is due to the electron withdrawing properties of the Ts group. The results also indicate that the DPEN analogues generally have significantly higher activities than their cyclohexyl derivatives.

CHAPTER 3

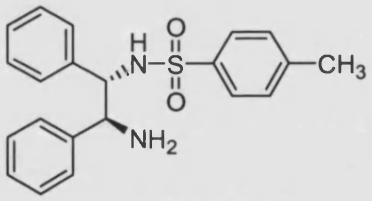
NOVEL AMINE BASED LIGANDS VIA S_NAR CHEMISTRY

3.1 MONO-ARYLATED DIAMINE LIGANDS

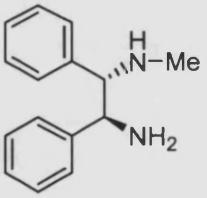
We wished to investigate the effect of more electron withdrawing substituents on the activity of mono-substituted diamine ligands. The success of the Noyori ligand and the observed higher activity of the aryl sulphonamide ligand (**50**) compared to other ligands prepared in the chapter 2, begged the question of whether electronic effects were the key determinant of ligand activity. Noyori noted that Ts-DPEN (**23**) is more active than the more electron rich $NH(CH_3)$ analogue **59**[44], even though the two ligands showed similar enantioselectivities in the transfer hydrogenation reaction.



50

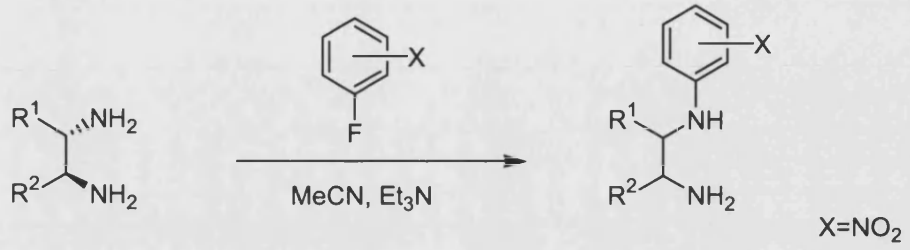


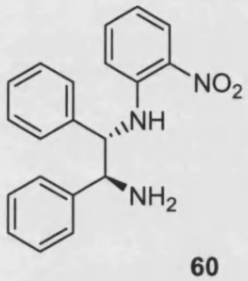
23



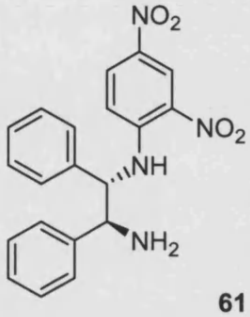
59

It was hoped that the effect of electron withdrawing substituents could be investigated by preparing a range of mono-substituted nitro aryl diamines by nucleophilic aromatic substitution (scheme 3.1). The introduction of mono- and di-nitro aryl derivatives would lead to ligands with an increasingly electron deficient secondary amine.

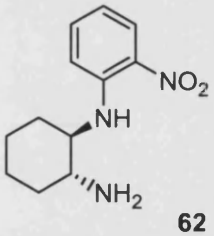




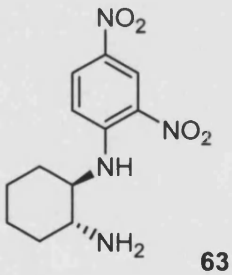
60



61



62



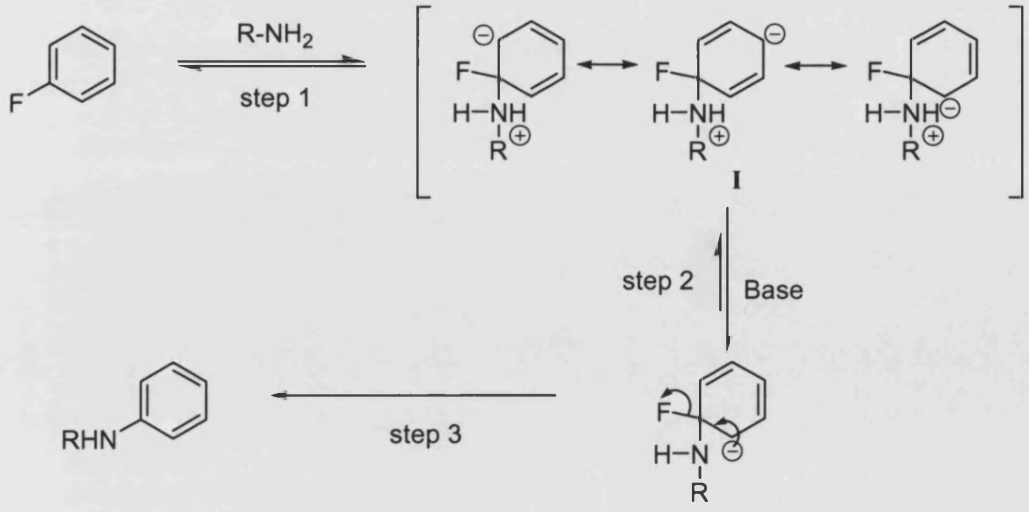
63

Scheme 3.1

The ligands were prepared by reacting aryl fluoride with diamine in the presence of a base. Little difference was observed between using MeCN or THF as the solvent. However, the choice of base proved to be important in

optimising the reaction yields. Lower yields were observed when using NaO*t*-Bu as opposed to K_2CO_3 or Et_3N. Attempts to form the 2,4,6-trinitrophenyl substituted analogues resulted in very poor yields due to uncontrollable formation of bis-arylated by-products. The three-step mechanism is illustrated in scheme 3.2. The first step, usually rate determining, step involves the addition of the amine nucleophile to the aryl halide forming a charged intermediate (**I**) while the second and third steps, involve the abstraction of a proton from the ammonium intermediate and ejection of fluoride respectively.

The rate of S_NAr reactions increases with greater electronegativity of the halide, due to reduced electron density of the adjacent carbon, making aryl fluorides more reactive than chlorides and bromides. However, simple aryl halide species are usually not sufficiently activated to undergo nucleophilic substitution and therefore require additional electron withdrawing groups around the ring.

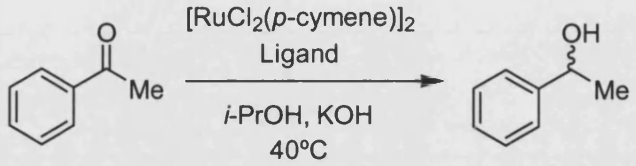


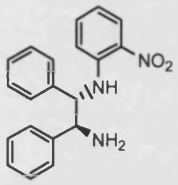
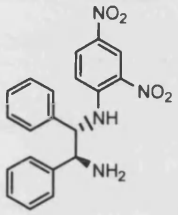
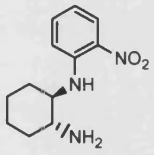
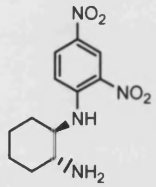
Scheme 3.2 Mechanism of Aromatic nucleophilic substitution

Such substituents stabilise the negative charge of the intermediate which is mostly localised at the *ortho* and *para* positions. Thus electron withdrawing groups *ortho* or *para* to the halide are most effective. Nitro groups are commonly used because these are both electron withdrawing and allow for charge stabilisation through resonance delocalisation (see scheme 3.3).

Scheme 3.3

The ligands were tested in the ruthenium catalysed transfer hydrogenation reaction (see table 3.1). The conversions were very poor, with less than 10% conversion in each case after 40 hours of reaction.



ligand structure	ligand	% conversion
	**60**	1
	**61**	6
	**62**	5
	**63**	1

conditions: See procedure B

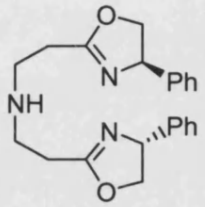
Table 3.1 Transfer hydrogenation results after 40 hours using nitroaryl diamines

The failure of these ligands probably stems from the nitro functionality. While these groups were required for the activation of the aryl species to aromatic

nucleophilic substitution, it is possible that the decreased activity of the ruthenium catalyst was caused by the complexation of the nitro groups with the metal centre, effectively poisoning the catalyst.

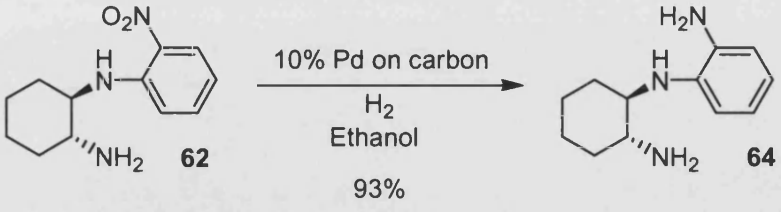
3.2 TRIDENTATE LIGANDS IN TRANSFER HYDROGENATION

Some success in the transfer hydrogenation of ketones has been achieved using tridentate ligands in conjunction with $Ru(PPh_3)_3Cl_2$. In particular, Zhang and co-workers[18] achieved high enantioselectivities using a bis-(oxazolinyl)amine ligand (**21**) with which 1-phenylethanol was obtained in up to 97% ee.



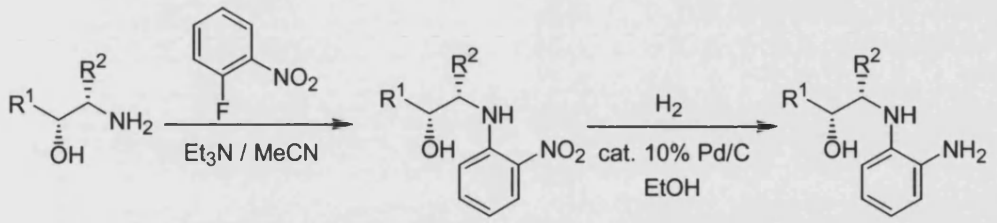
21

Following the disappointing results achieved with the 2-nitrophenyl diamine ligands, we wished to investigate whether reducing the nitro functionality to an NH_2 group would result in a more active triamine ligand. **62** Was reduced at room temperature using 10% Pd on carbon and hydrogen gas to give the desired tridentate ligand **64** (scheme 3.4).

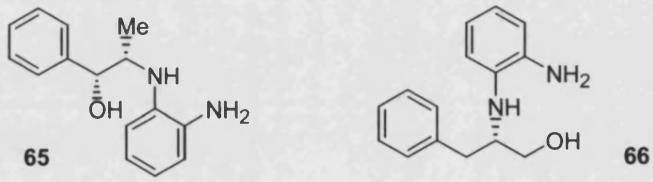


Scheme 3.4 Synthesis of **64**

This methodology allows for a high degree of diversity in the chiral backbone and two amino alcohol derivatives (**65** and **66**) were also prepared in similar fashion (see scheme 3.5).



Ligands Prepared;



Scheme 3.5 Preparation of ligands **65** and **66**

Ligand **65** was found to be quite unstable with discoloration occurring quite rapidly even when stored at 4°C. Tlc showed degradation products forming, though the nature of these was not investigated.

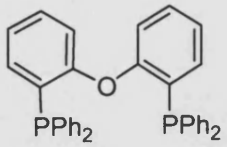
Though the ligands lacked C_2-symmetry, unlike **21**, it was thought that complexation to the metal may be influenced by steric factors, ensuring that the ligand complexes in a single preferred geometry.

The ligands were screened in the transfer hydrogenation of acetophenone at 82°C in isopropanol using 5 mol% of $Ru(PPh_3)_3Cl_2$. Ligand **66** gave no

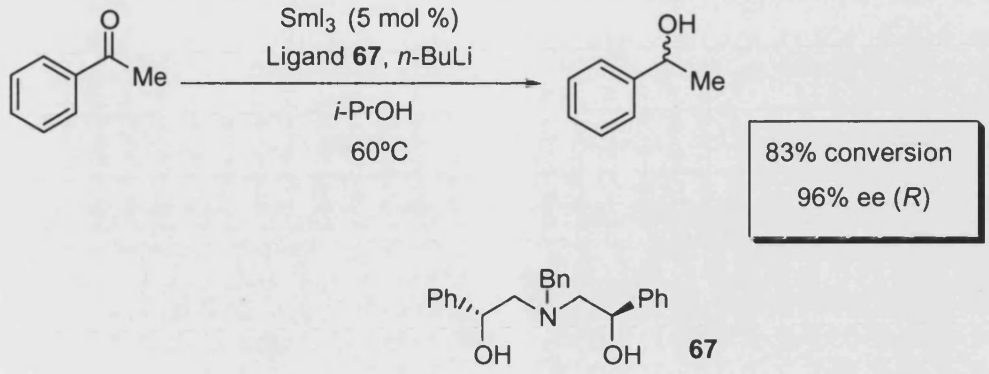
significant product formation after 1 day, and while triamine **64** showed some reactivity with a conversion of 88% after 15 hours, the enantioselectivity was low at 14% ee (*S*).

3.3 1,5-DIAMINE LIGANDS

The vast majority of diamine and amino alcohol ligands described in the literature for transfer hydrogenation are α,β-bidentate ligands. These usually form 5-membered chelate structures around a metal. We wished to investigate whether mono-*N*-tosylated 1,5-diamine ligands could act as active catalysts in the reaction by forming an 8-membered metal chelate. Though there have been no 8-membered metal chelates used in transfer hydrogenation, 1,5-bisphosphine ligands such as bis[2-(diphenylphosphino)phenyl]ether (DPEphos) have been used in the palladium catalysed amination reaction[45] and Evans[46] has shown that ligand **67** is active in the samarium catalysed asymmetric Meerwein-Pondorf-Verley reduction of ketones (scheme 3.6).

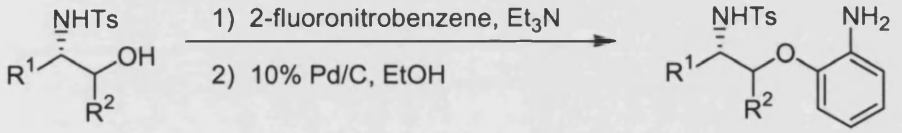


DPEphos

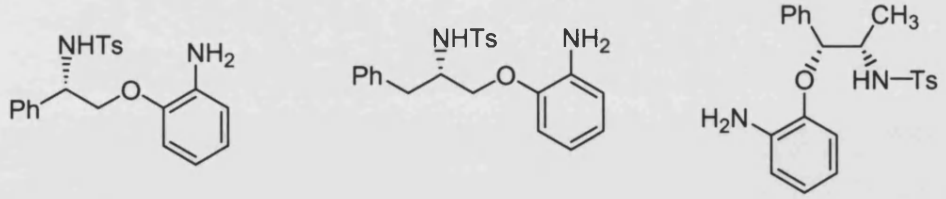


Scheme 3.6

To investigate whether a 1,5-mono-*N*-tosylated diamine would be effective a small library was prepared (see scheme 3.7).



Ligands prepared;



68 **69** **70**

Scheme 3.7

These ligands were screened in the transfer hydrogenation of acetophenone using [(*p*-cymene)$RuCl_2$]$_2$ at 40°C with a 5 mol% loading of Ru. However, the catalysts failed to give any significant conversion under these conditions (see table 3.2).

Ligand	% Conversion (16 hours)
68	1
69	1
70	0

Reaction conditions: See experimental conditions A

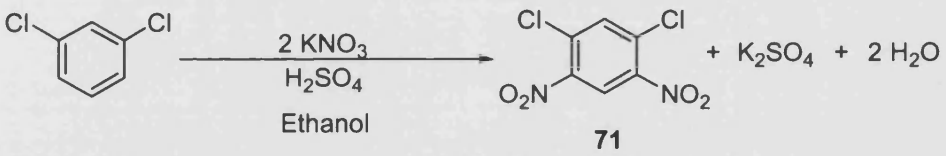
Table 3.2 Results from transfer hydrogenation of acetophenone using 1,5-diamine based ligands

Raising the temperature to 60°C, ligand **68** gave a conversion after 1 day of 49% but unfortunately with a near racemic product (3.6% ee (*R*)). It is possible that the ligands may be tridentate but no further screening was carried out after the poor results from the initial screen.

3.4 AMINO ALCOHOLS ON A NOVEL LIGAND BACKBONE

Enantiopure 1,2-amino alcohols have been effective ligands in the catalysis of a number of asymmetric reactions and, in particular, have been highly effective ligands for the acceleration of the ruthenium catalysed transfer hydrogenation of ketones.[25-27]

We wanted to investigate whether we could develop amino alcohol based ligands via S_NAr chemistry. We chose 2,4-dichloro-1,5-dinitrobenzene (**71**) (scheme 3.8) as a novel backbone which is very active towards S_NAr reactions.

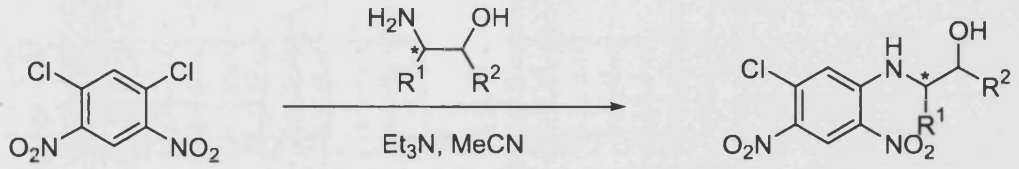


71

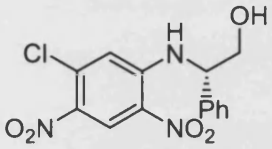
Scheme 3.8

The nitro functionality may be expected to give the ligand some water solubility in its complexes and it was hoped that the reaction could be controlled to give substitution at either one or both C-Cl bonds.

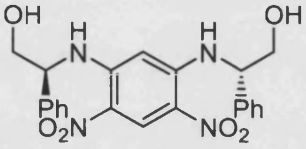
The ligands were prepared in anhydrous acetonitrile using triethylamine to trap the HCl formed (scheme 3.9). With the amino alcohols the amine was the attacking nucleophile in all cases and this was confirmed by ^{1}H-nmr where the NH peak was visible as a doublet at δ 8-9 ppm.



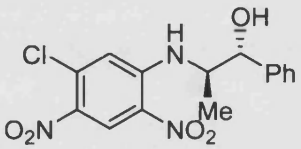
Ligands prepared;



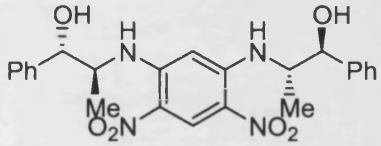
72



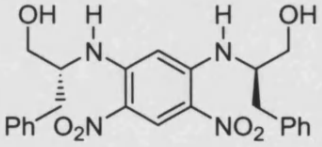
73



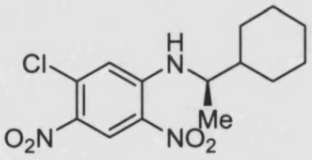
74



75



76



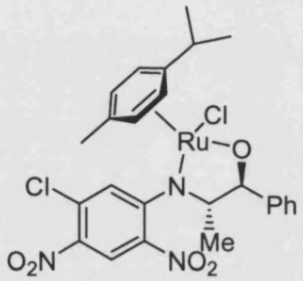
77

Scheme 3.9 Preparation of ligand library

Mono substitution proved easy to achieve. This may be due to the electronegativity difference between chlorine and nitrogen (3.16 to 3.04 Paulings), causing the second substitution to be less favoured than the first. This activity difference was sufficient to allow for control over the substitutions, which was vital to allow for potential ligand optimisation. Thus the introduction a second enantiopure group to act as a chiral modifier, or the

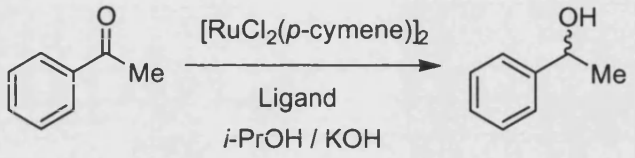
introduction of an amino acid ester (to increase the water solubility of the ligand, permitting catalyst recovery by aqueous extraction) could be considered as possible methods for optimisation.

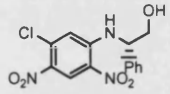
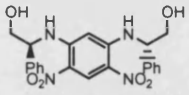
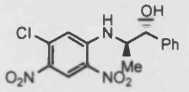
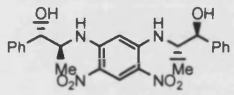
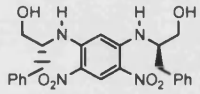
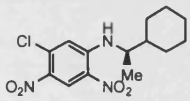
It was envisaged that the ligand would complex to the metal centre of the *p*-cymene ruthenium chloride to form a well precedented 5-member chelate as shown in scheme 3.10 and that the bis-amino alcohol ligands may form bis-ruthenium catalyst species.



Scheme 3.10 Proposed structure of 5-membered chelate catalyst precursor

For the purposes of the ligand library however, it was important that the activity of the initial library was tested prior to any further functionalisation. Results from the transfer hydrogenation of acetophenone were poor, with both low conversions and low enantioselectivities obtained (see table 3.3) and so no further development of this library was carried out.



Structure	Ligand	% Conversion/ (% ee)
	**72**	8
	**73**	8
	**74**	15 (0)
	**75**	11
	**76**	12
	**77**	20 (6)

conditions: see experimental section 6.7- Procedure B

Table 3.3 Results from transfer hydrogenation at 40°C after 40 hours.

The inactivity of these ligands could be a result of deactivation of the catalyst by the *ortho*-nitro groups. These groups could complex to the ruthenium centre thus deactivating it. It is also possible that the nitrophenyl group electronically deactivates the amino alcohol complex. Furthermore, it was later found, during

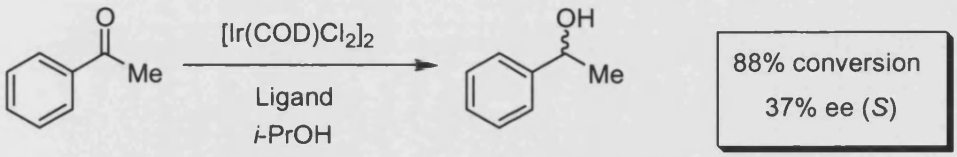
the work with amino alcohols (see chapter 5), that the substituent on the amine terminus of an amino alcohol should be electron donating (e.g. alkyl groups) to achieve highly active Ru catalysts.

CHAPTER 4

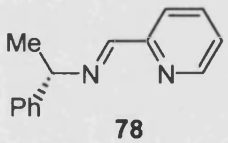
IMINO ALCOHOL LIGANDS IN TRANSFER HYDROGENATION

4.1 INTRODUCTION

A number of groups have reported the use of ligands incorporating imine functionality for the transfer hydrogenation of ketones. Several ligands acting as bis-imino chelates have been tested in the reduction of acetophenone. An early example was reported by Zassinovich *et al.*[47] who used (*S*)-2-pyridinal-1-phenylethylimine (**78**) in conjunction with $[Ir(COD)Cl_2]_2$ to give (*S*)-1-phenylethanol in 88% conversion and 37% ee (*S*) (scheme 4.1).



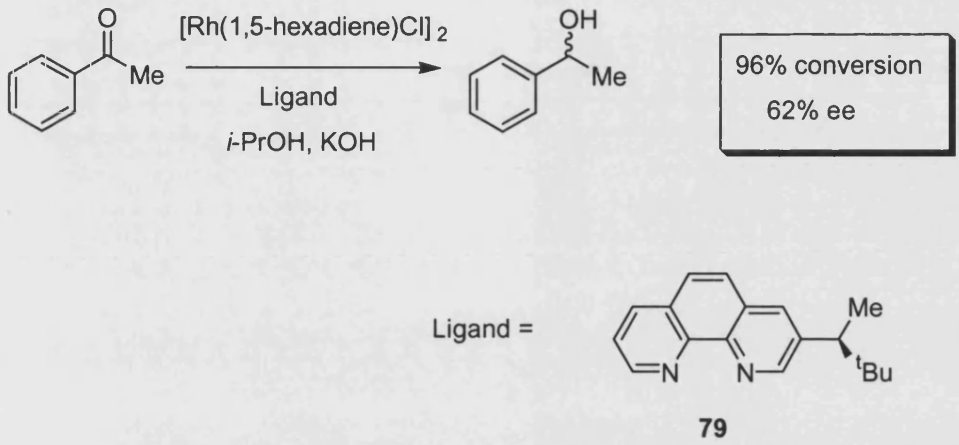
Ligand =



78

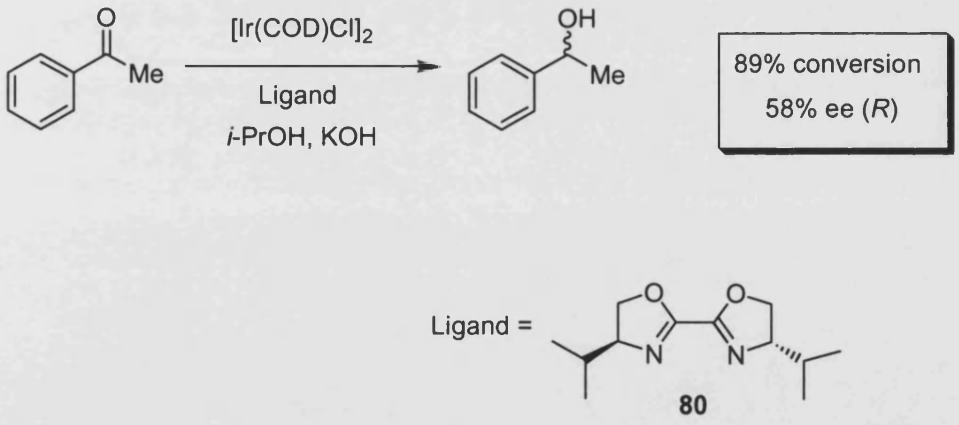
Scheme 4.1

While the selectivity was quite low with acetophenone, the reduction of ketones such as *t*-butyl phenyl ketone resulted in the corresponding alcohol in high yield (94%) and a greater ee of 80% (*S*). Soon after this Gladiali *et al.*[48] published results from the use of optically active phenanthrolines in conjunction with a Rh(I) catalyst. Using phenanthroline **79**, the catalyst delivered 1-phenylethanol in up to 96% conversion with 62% ee (scheme 4.2).



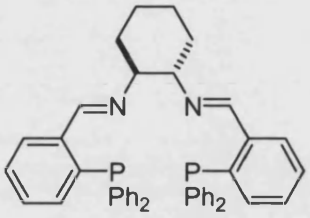
Scheme 4.2

The use of bis-oxazolines in the Ir catalysed reaction was investigated by Pfaltz *et al.*[49] using **80**. This ligand proved moderately effective, resulting in a conversion to (*R*)-1-phenylethanol of 89% with an ee of 58% (scheme 4.3).

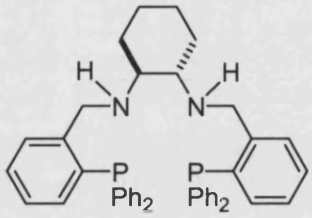


Scheme 4.3

Later on, a number of mixed functionality imine based ligands were tested. Noyori[50] investigated the effectiveness of a bis-imino phosphine ligand (**81**).

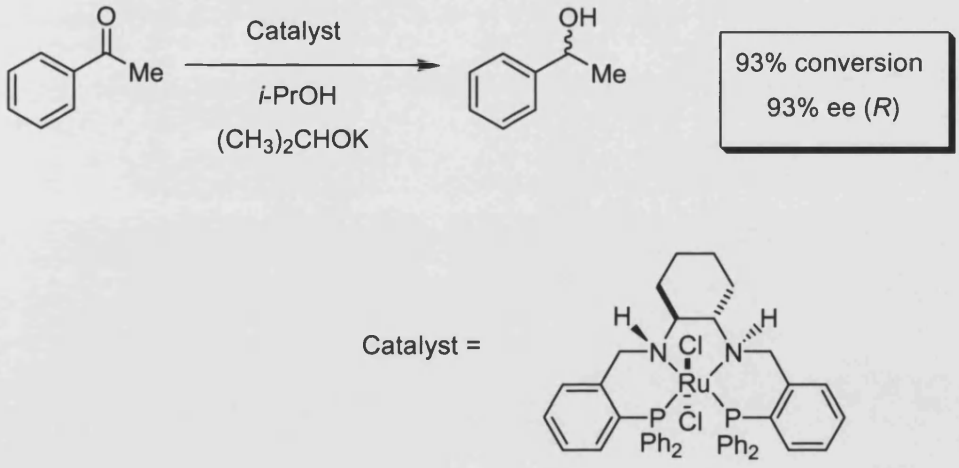


(S,S)-**81**



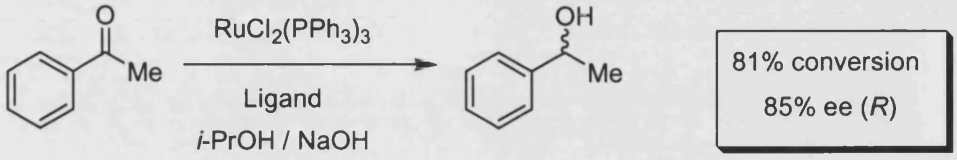
(S,S)-**82**

The ligand showed poor activity in the Ru(II) catalysed transfer hydrogenation of acetophenone, resulting in a very low conversion (3%), while the amino phosphine analogue (**82**) was more reactive, giving a conversion of 93% and an ee of 93% (*R*) (scheme 4.4).

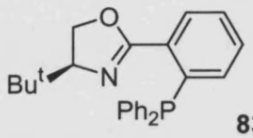


Scheme 4.4

Noyori reasoned that this was due to the requirement for an acidic hydrogen in the form of an NH moiety. However, in the same year, Helmchen[51] reported the successful use of an imidato phosphine ligand, **83**, which reduced acetophenone to (*R*)-1-phenylethanol in up to 85% ee (see scheme 4.5).



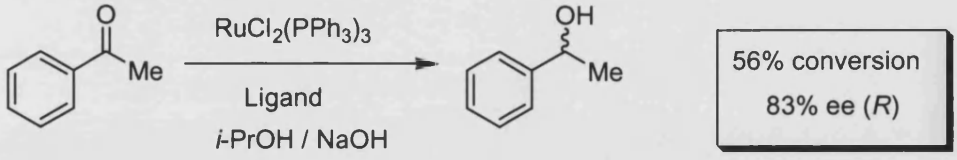
Ligand =



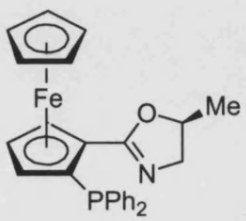
83

Scheme 4.5

Uemura *et al.*[52] reported the use of another imidato phosphine ligand **(84)** in the Ru(II) catalysed transfer hydrogenation of acetophenone and obtained 1-phenylethanol in up to 56% yield and 83% ee (*R*).



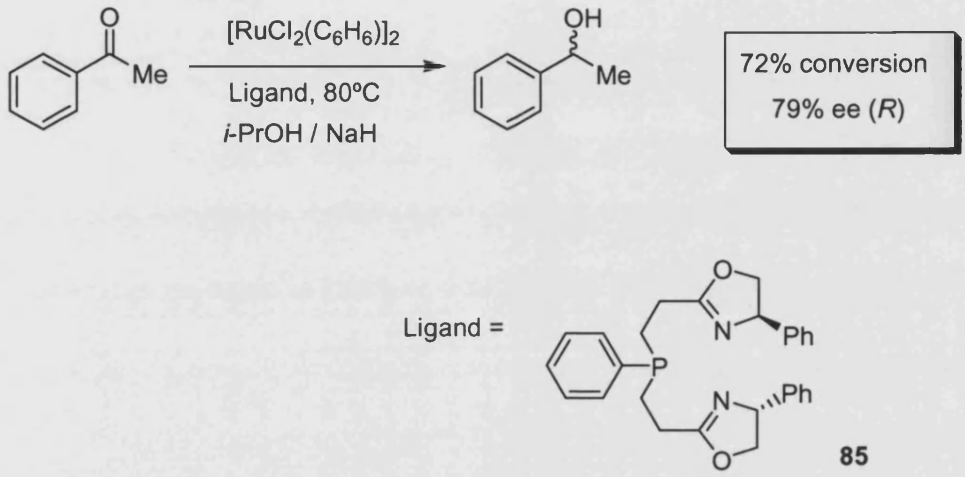
Ligand =



84

Scheme 4.6

Zhang[53] developed a NPN-type tridentate ligand (**85**) incorporating two oxazoline groups attached via a spacer to a phenyl phosphine group. He found that the ligand was effective in the reduction of acetophenone, giving the corresponding alcohol in good yield and 79% ee (scheme 4.7).



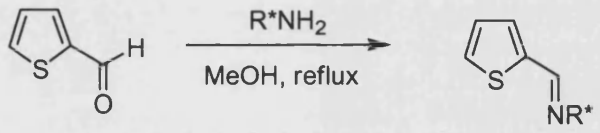
Scheme 4.7

4.2 LIBRARY PREPARATION

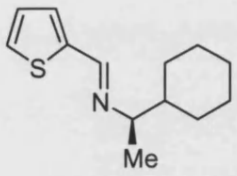
There was clear precedent for imine based ligands being effective in the transfer hydrogenation reaction. However, to the best of our knowledge, the use of imino alcohol ligands had not been reported although considerable evidence exists showing amino alcohol ligands[54] to be active ligands.

To investigate this possibility, a library of imines and imino alcohols derived from readily available thiophene carboxaldehydes and amino alcohols were prepared *via* a facile condensation reaction in refluxing anhydrous methanol

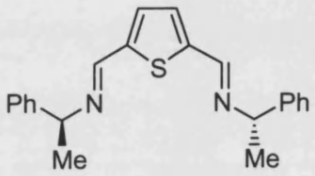
(see scheme 4.8). The reactions proceeded to completion in all cases to give the imino alcohol ligands in quantitative yields.



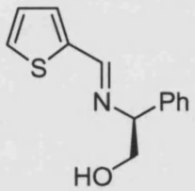
Ligands prepared;



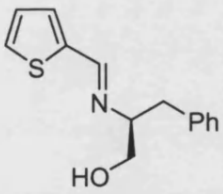
86



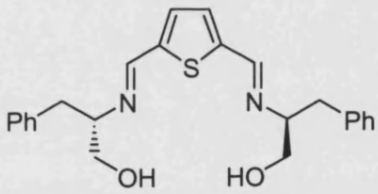
87



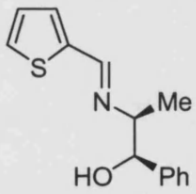
88



89



90



91

Scheme 4.8

The ligands would be expected to form a 5-membered chelate ring with the ruthenium complex as shown in figure 4.1.

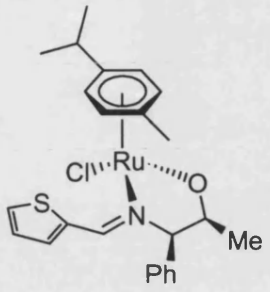
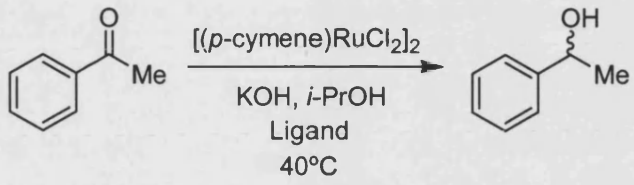


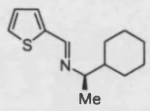
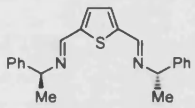
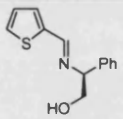
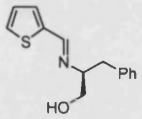
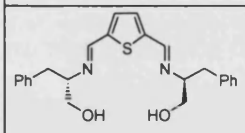
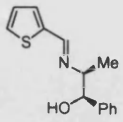
Figure 4.1

Though there is sufficient evidence for the formation of such complexes, it was unclear what orientation the ligand would adopt. We speculated whether or not there may be any weak interaction between the lone pair on the sulfur atom and the empty *d*-orbital on the ruthenium and also whether any such interaction would result in either a significant loss in activity or an increase in ee. We expected that the thiophene moiety would at least act as a steric block, influencing the approach of the incoming ketone and orienting it relative to the ruthenium core.

Initial testing of the ligands in ruthenium catalysed transfer hydrogenation showed that the imino alcohol ligands were active in the reaction, with the reactions going to completion within 2 hours at 40°C (see table 4.1). The imines however showed very poor activity, with very low conversions observed even after 40 hours. The selectivity with imine ligand **86** was also very low, with the product being nearly racemic. The enantioselectivities

obtained from the imino alcohols varied considerably ranging from only 10% ee with ligand **89** to 70% ee with ligand **91**.



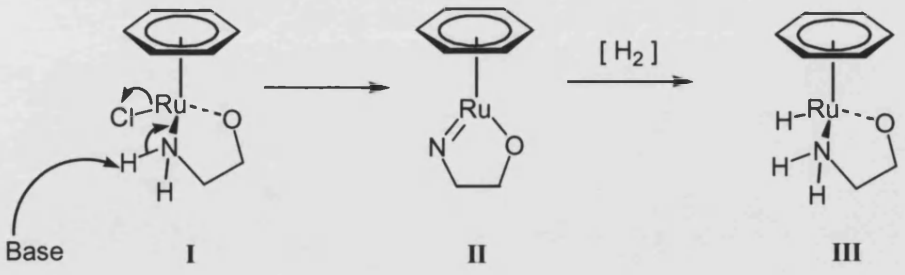
Structure	Ligand	% conversion [% ee] after 2 hours	% conversion [% ee] after 40 hours
	**86**	4 [n.d.]	15 [<1 (*S*)]
	**87**	2 [n.d.]*	n.d.
	**88**	94 [20 (*R*)]	93 [19 (*R*)]
	**89**	95 [10 (*S*)]	93 [10 (*S*)]
	**90**	95 [13 (*S*)]	94 [13 (*S*)]
	**91**	86 [70 (*R*)]	88 [62 (*R*)]

*Reaction after 3 hours

Table 4.1 Results (GC) with imine and imino alcohol ligands after 2 and 40 hours at 40°C

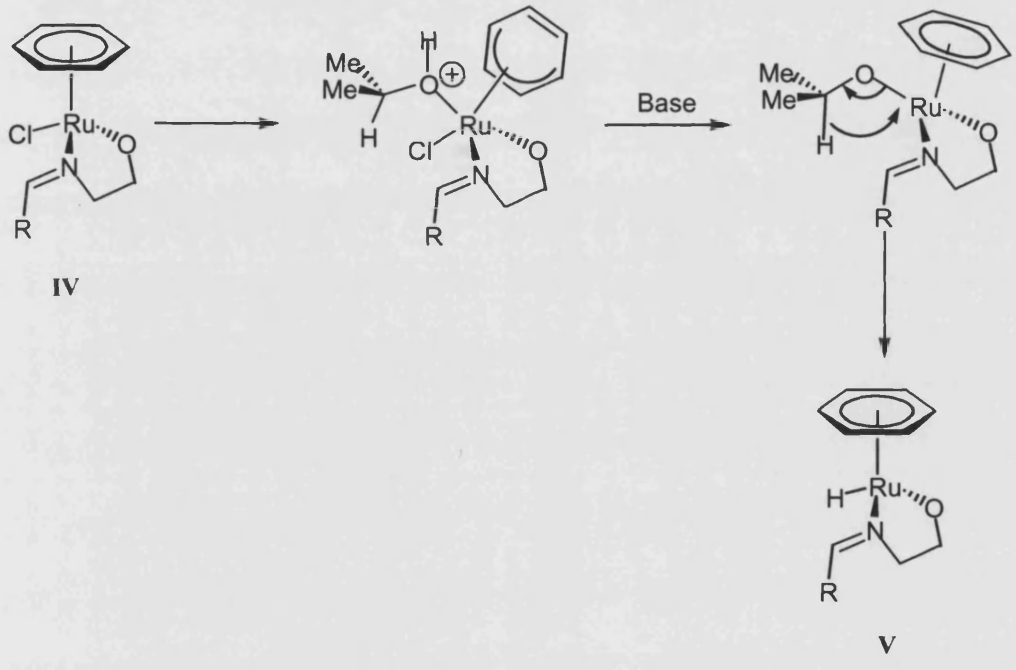
After elongated reaction times (40 hours) there was a slight fall off in enantioselectivities, possibly due to back reaction, a process known to occur when using isopropanol as the hydrogen source. It is for this reason that a dilute substrate solution is used. Avoiding the use of the isopropanol/KOH conditions and switching to the Et_3N/formic acid mixture instead would eliminate this problem, the reaction then being essentially irreversible. However, attempts to use this system with **91** gave very low conversions, probably due to catalyst instability in this medium.

Imino alcohols had proven effective ligands for the ruthenium catalysed reaction. However, the mechanism when using imino alcohols cannot be identical to that described for amino alcohol catalysts (see scheme 1.11). In this proposed mechanism the first step is the base promoted elimination of HCl from **I** to give **II** which then accepts an equivalent of hydrogen to generate the active Ru-H catalyst **III** (see scheme 4.9).



Scheme 4.9

However, with imino alcohol ligands this step is not possible due to the nitrogen being aprotic. We believe that isopropanol promotes the elimination of HCl, by the mechanism shown (scheme 4.10), to give the ruthenium hydride catalyst **V**.

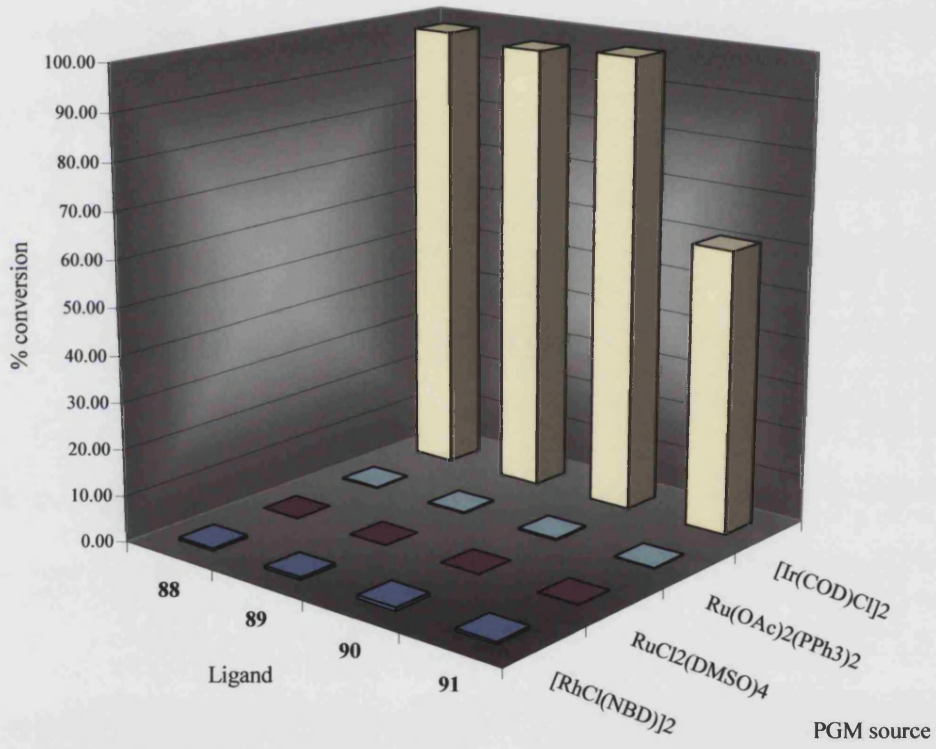


Scheme 4.10

The active imino alcohol ligands were then screened across a range of platinum group metal (PGM) precursors, namely, $[Ir(COD)Cl]_2$, $[RuCl_2(DMSO)_4]$, $[Rh(NBD)Cl]_2$ and $Ru(OAc)_2(PPh_3)_2$. While there is some literature evidence for the use of $[Ir(COD)Cl]_2$[55] and $[Rh(NBD)Cl]_2$[56], the other PGM sources have not been used in the reaction previously and we wished to investigate whether they were suitable and what effect the choice of metal source would have. The

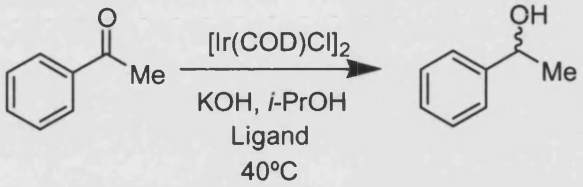
reactions again were carried out at 40°C and the results are summarised in graph 4.1.

As can be seen, only the reactions with $[Ir(COD)Cl]_2$ showed any significant conversion in the transfer hydrogenation of acetophenone.



Graph 4.1 Transfer hydrogenation of acetophenone at 40°C using different PGM sources

The results with $[Ir(COD)Cl]_2$ after 3 hours are shown in table 4.2. The conversions were high but the enantioselectivities were less than when using $[(p\text{-cymene})RuCl_2]_2$. In particular, **91** gave an ee of only 23% using Ir compared to an ee of 70% with Ru under similar conditions.



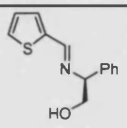
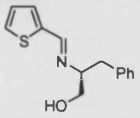
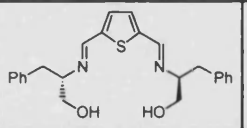
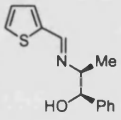
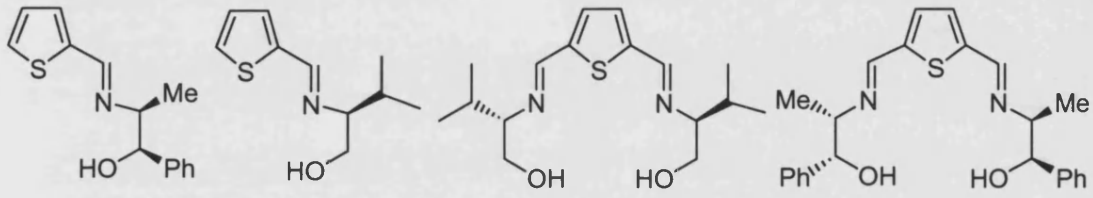
Structure	Ligand	$[Ir(COD)Cl_2]$	$[(p\text{-cymene})RuCl_2]_2$
		% conv. [% ee]	% conv. [% ee]
	**88**	98 [15 (*R*)]	94 [20 (*R*)]
	**89**	96 [7 (*R*)]	95 [10 (*S*)]
	**90**	98 [4 (*R*)]	95 [13 (*S*)]
	**91**	61 [23 (*R*)]	86 [70 (*R*)]

Table 4.2 Results from the Ir catalysed transfer hydrogenation

The configuration of the alcohol product with the iridium catalyst was reversed with ligands **89** and **90,** affording predominantly the *R*-alcohol, as opposed to the ruthenium catalyst where the major product was (*S*)-1-phenylethanol. This enantioselection was not reversed with ligands **88** and **91** however.

The imino alcohols had shown a high degree of activity in the reaction and it was decided that they warranted further optimisation. The ligand design allows for a degree of diversity and modifications were easily achieved by changing the aldehyde and amino alcohols used.



91 **92** **93** **94**

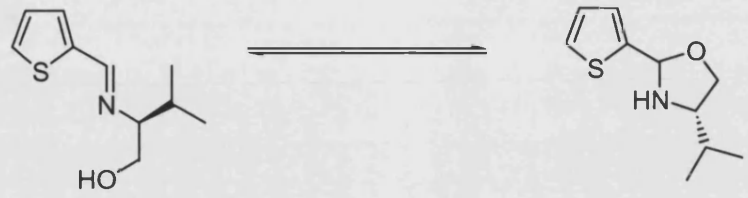
Two new ligands (**92** and **93**) were prepared from (*S*)-valinol, and a C_2-symmetric bis-imino alcohol ligand (**94**) was prepared from (1*R*,2*S*)-norephedrine. Results from the transfer hydrogenation of acetophenone at 40°C are summarised in table 4.3.

	Ligand	**% conversion**	**% ee (config.)**
valinol ligands	**92**	98	10 (*S*)
	93	>95	9 (*S*)
norephedrine ligands	**94**	49	72 (*R*)
	91	86	70 (*R*)

Table 4.3 Results from the reduction of acetophenone at 40°C using mono- and bis- imino alcohols

As can be seen from the results, the enantioselectivities of the bis-imino alcohol ligands are not significantly different from those of their mono-analogues, when comparing **92** and **93** or **91** and **94**. However, the reaction did not go to completion using the bis-norephedrine ligand **94**, even after 24 hours where the conversion was nearly identical (47%), suggesting that the second imino alcohol group only serves to lower activity, and possibly poisons the catalyst. Due to the similarity in ee obtained, it is probable that the active catalyst has the metal bound to one of imino alcohol units, the second imino alcohol either being redundant or complexing to a second ruthenium atom. Ligands **92** and **93** were active ligands in the reaction but resulted in low ee's which fell off over an extended period of time. The norephedrine analogues gave the highest selectivity of the catalysts screened, though it is possible that other chiral amino alcohols could lead to higher enantioselectivities.

An interesting aspect of these imino alcohols appeared while preparing them. In some cases (e.g. **92** and **93**), there appeared to be a minor impurity present in the ^{1}H-nmr when run in $CDCl_3$ which was inconsistent with either of the starting materials. The impurity was not due to any imine E/Z isomerism as only 1 peak could be seen for the imine proton by nmr. We believe that the imine isomerises in solution to give a mixture of free imine and oxazolidine (see scheme 4.11).



Scheme 4.11 Formation of oxazolidine in solution

The ^{1}H-NMR peaks for the minor impurity fitted this assumption with peaks seen for both diastereomers of the oxazolidine (see section 6.5). However, the extent of this tautomerisation was dependent on the solvent used; **92** showed that the minor isomer accounted for *ca.* 15% of the total in $CDCl_3$ while it was present in negligible quantities in both d_3-MeCN and CD_3OD.

The initial product formed is however the free imine and this was shown by the X-ray crystal structure of **92** (see figure 4.2). The C-N bond between C(5) and N(1) has a length of 1.258Å, which is consistent with a C=N double bond (1.28Å) and much shorter than a typical C-N single bond (1.47Å).

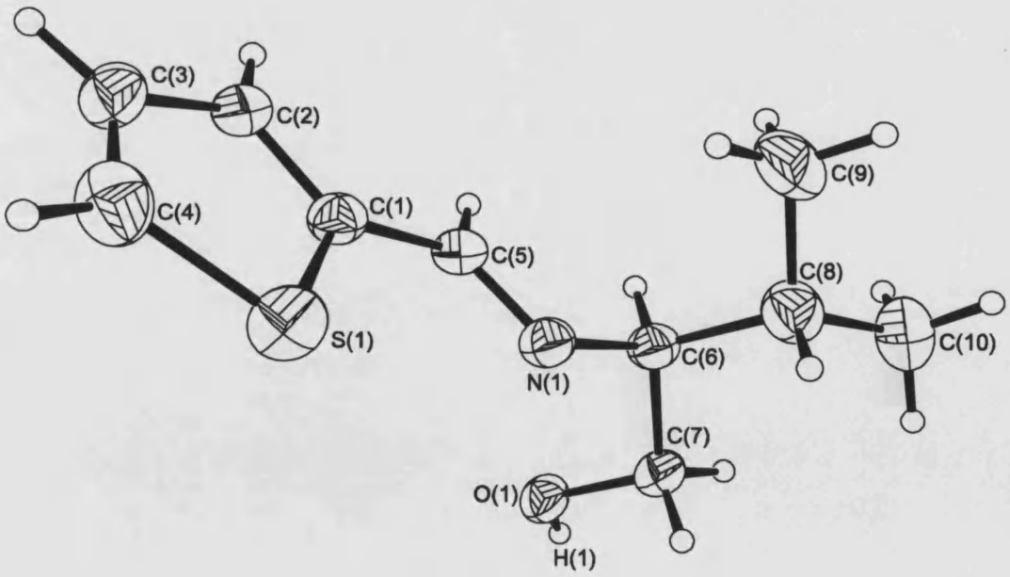
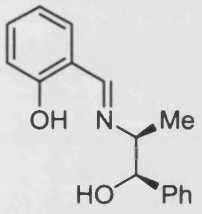


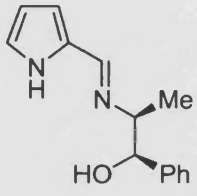
Figure 4.2 Crystal structure of **92**

It is probable that the oxazolidine formed in $CDCl_3$ because the solvent was sufficiently acidic to catalyse the interconversion.

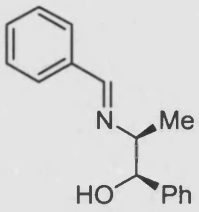
Attention next turned to the role of the arene moiety (thiophene), if any, in the catalyst. Though it was believed that it exerted merely steric influences, the possibility of a weak interaction between sulfur and ruthenium could not be ruled out. Thus, it was decided to investigate whether such interactions could be of benefit to the reaction. To this end, a small number of imine derivatives of norephedrine were prepared with varying aryl groups.



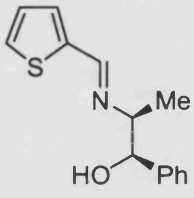
95



96



97



91

Ligands **95** and **96** each had a heteroatom in close proximity to the imine nitrogen while **97** had no heteroatom. The transfer hydrogenation results from these three ligands are given in table 4.4.

Ligand	% conversion	% ee
95	46	77 (*R*)
96	7	–
97*	96	83 (*R*)
91	92	76 (*R*)

*Ligand prepared *in situ* - result after 2 hours of reaction

Table 4.4 Results using after 16 hours at 20°C.

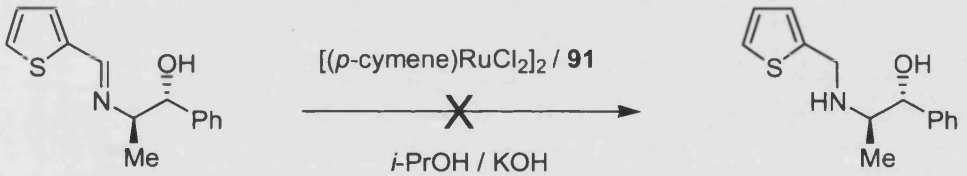
There is a lowering in activity in cases where there is a third chelating group on the ligand. However, most ligands showed some degree of activity, with even the phenolic ligand giving a moderate conversion of 46% at room temperature after 16 hours. The enantioselectivities obtained in all cases were above 70%. The notable exception was pyrrolic ligand **96**, which formed a very unreactive catalyst. The pyrrole NH was unlikely to complex to the metal centre, but the NH is rather acidic (pK_a *ca.*17) and so it can be deprotonated by KOH in the reaction medium, thus enabling complexation of the pyrrole nitrogen anion to the metal centre. The low reactivity is probably due to this complexation. Of the most active ligands, **91** and **97**, there was a difference in the enantioselectivity of the catalysts, with phenyl **97** giving a slightly higher ee than either thiophenyl **91** or phenolic **95**. Therefore, the weak binding of the third heteroatom, if present, had no positive effect on the enantioselectivity of the catalyst, but had a detrimental effect on reactivity.

Attempts to increase the enantioselectivity with these ligands further, by lowering the temperature to as low as 0°C, had limited success. Ligand **91**, at 0°C, gave (*R*)-1-phenylethanol in 84% ee but with a slow reaction resulting in a conversion of only 60% and that after 6 days. Ligand **97** was more active than **91**, resulting in conversion to 1-phenylethanol of 93% within 2 hours, using 5 mol% Ru at 10°C, with an ee of 86.7% (*R*).

Though we believed that the imino alcohol was the active ligand there was a possibility that the imino alcohol was reduced *in situ* and was therefore not in fact the active catalyst. It is well known that the reduction of imines is possible by transfer hydrogenation.[57] It may be imagined that initial reduction of the

ruthenium bound imino alcohol ligand, resulting in a Ru-amino alcohol complex, could serve as the active catalyst. If this occurred, then a one-pot reaction could occur in which the ligand, the pre-catalyst and then the catalyst would form in sequence. We knew that imino alcohols could be formed in isopropanol and that the reaction could be carried out *in situ*.

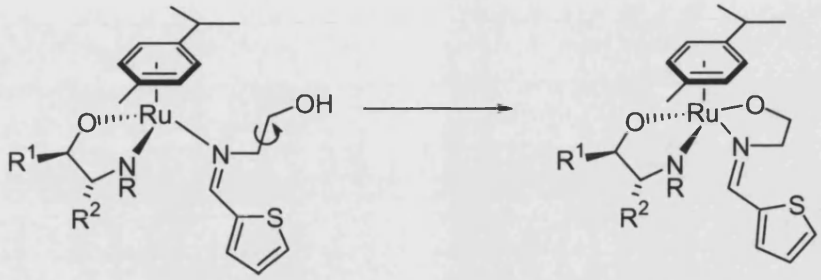
We wanted to investigate whether reduction, or perhaps hydrolysis of the imine bond was taking place. We first attempted to reduce imino alcohol **91** by transfer hydrogenation using catalytic ruthenium but this failed to give any detectable reduction products (scheme 4.12), indicating that imino alcohols are not readily reduced via this procedure.



91 **99**

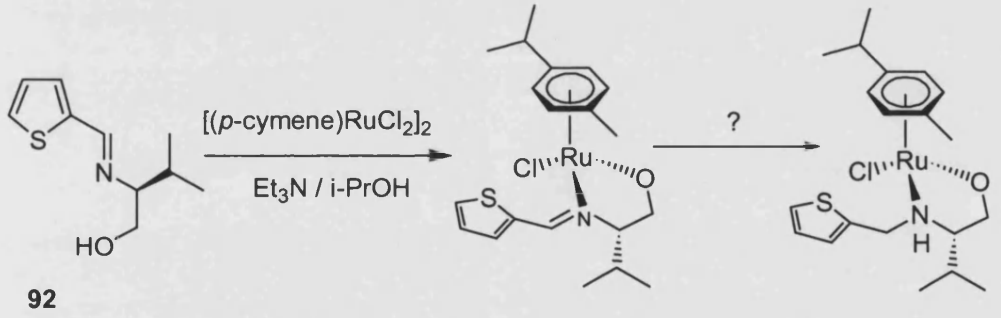
Scheme 4.12 Attempted reduction of **91**

One possible reason for this failure to reduce an β-imino alcohol is a deactivating effect from the hydroxy moiety on the catalyst (scheme 4.13). If one considers the imine bound catalytic species, the oxygen atom of the imino alcohol could bind to the ruthenium to form a 5-membered chelate ring effectively poisoning the catalyst by blocking all available ruthenium *d*-orbitals necessary for catalysis.



Scheme 4.13

Attempts were then made to investigate whether the imino function was reduced while complexed to stoichiometric ruthenium. $[(p\text{-Cymene})RuCl_2]_2$ and **92** were refluxed in isopropanol with two equivalents of triethylamine (see scheme 4.14).



92

Scheme 4.14

The reaction resulted in the formation of a complex with loss of the imine CH resonance peak in the NMR. There was no peak seen for the formation of hydrolysis products. Under the normal transfer hydrogenation conditions the same pattern was observed, with the imine peak being lost.

When the identical reaction was run in $CDCl_3$ the imine peak was not lost indicating that, in isopropanol at least, reduction of the imine bond may be occurring.

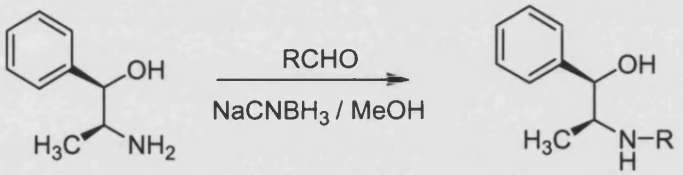
Thus we decided to investigate amino alcohol ligands in transfer hydrogenation and a number of analogues were prepared and tested. This matter is discussed in the next chapter.

CHAPTER 5

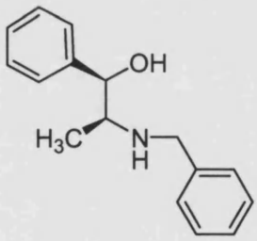
AMINO ALCOHOL LIGANDS IN TRANSFER HYDROGENATION

5.1 DEVELOPMENT OF AN AMINO ALCOHOL LIGAND LIBRARY

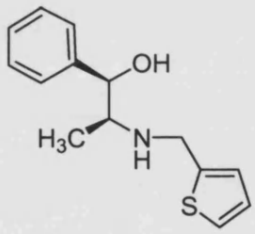
The most successful of the imino alcohol ligands tested were **91** and **97**. The corresponding amino alcohol analogues of these (**98** & **99**) were prepared, in moderate yields, by reductive amination (see scheme 5.1).



Ligands prepared:



98



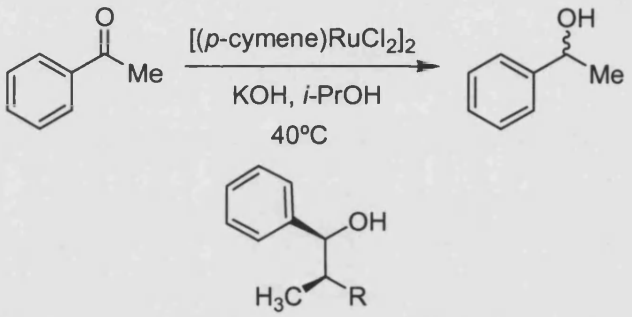
99

Scheme 5.1

These ligands were also active in the ruthenium catalysed transfer hydrogenation reaction at 40°C, but the enantioselectivities were greater than those from the corresponding imines (see table 5.1).

Enantioselectivities were increased substantially on lowering the reaction temperature from 40°C to 28°C, much more so than with the imino alcohols.

The ee's from both the imino and amino alcohol ligands were higher than comparable ee's from (1*R*, 2*S*)-norephedrine.



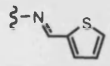
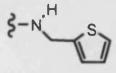
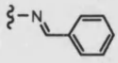
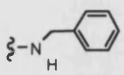
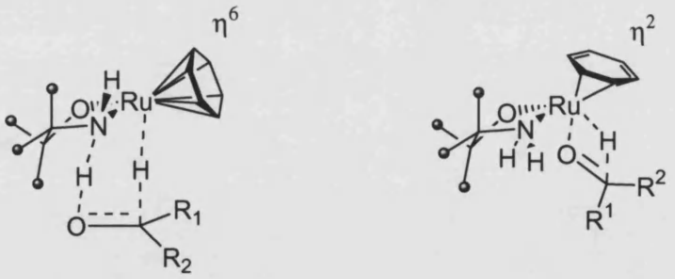
R	Ligand	Temp / °C	% Conv.	% ee (config.)
	**91**	40	96	65 (*R*)
		20	92	76 (*R*)
	**99**	40	97	83 (*R*)
		28	96	93 (*R*)
	**97**	40	93	80 (*R*)
		20	96	83 (*R*)
	**98**	40	93	79 (*R*)
		28	95	91 (*R*)
	**norephedrine**	40	96	58 (*R*)

Table 5.1

5.2 MECHANISTIC CONSIDERATIONS & RATIONALE FOR OBSERVED ENANTIOSELECTIVITY

5.2.1 Transfer hydrogenation mechanism using amino alcohol ligands

Recently there has been some debate over the exact mechanism of the ruthenium catalysed reaction when using amino alcohol ligands. Noyori[58] and Andersson[59] have, as a result of modelling calculations, suggested that the lowest energy pathway involves a mechanism in which no metal alkoxide is formed. Instead, the hydride and proton are transferred in a concerted manner via a 6-membered cyclic transition state (TS) **I** (figure 5.1). This differs from the mechanism described in scheme 1.11 where a 4-membered cyclic transition state **II** occurs.

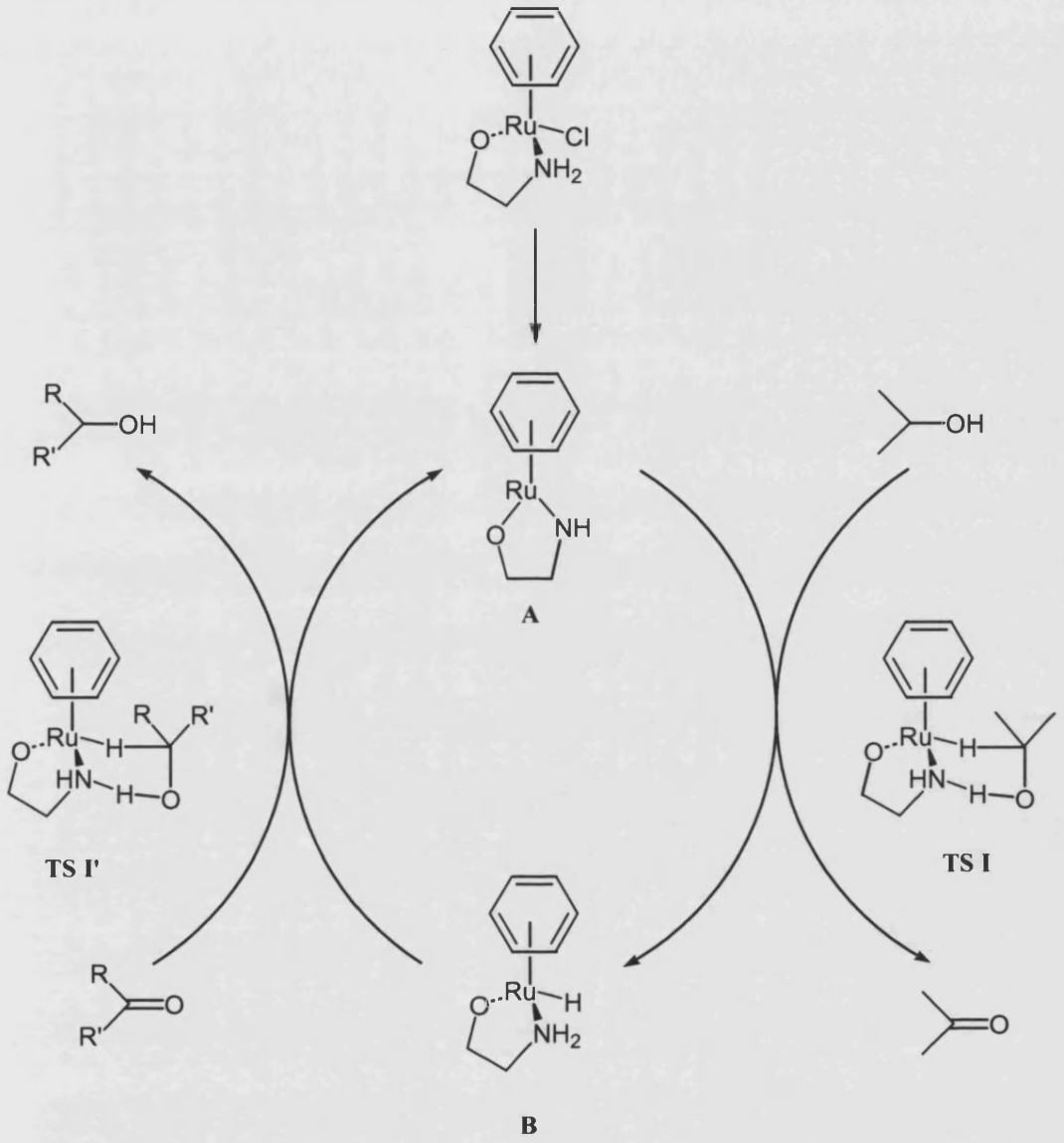


I **II**

Figure 5.1

The modelling calculations indicate that TS **I** has a lower activation energy than **II** (12.9kcal/mol vs. 20.1kcal/mol). Andersson suggested that in the alkoxide TS mechanism the aryl group hapticity changes during the reaction from η^6 to η^2 (rather than to the expected η^4) to accommodate the increase in coordination number. This change in hapticity is energetically unfavourable and results in the higher energy barrier of this pathway. Bearing this in mind, it is reasonable to assume that the reaction may proceed via TS **I** with the mechanism shown in scheme 5.2. The mechanism involves the formation of the $16e^-$ catalytic species **A** which accepts hydrogen from isopropanol via TS **I** to give the Ru-H species **B**. This in turn transfers hydrogen to the ketone substrate, via TS **I'**, to regenerate **A** and release the alcohol product.

This suggested mechanism is rather unique in transition metal mediated homogenous catalysis. In most catalytic reactions the ligand's function is to modify the electronic and steric properties of the metal. The catalysis usually involves initial complexation of the reagent (e.g. ketone) to the metal centre. The bond forming and breaking reactions then occur while the substrate remains complexed to the metal. The mechanism here however, exhibits metal-ligand bifunctional catalysis, in which both the metal and the ligand are actively involved in the reaction. As a consequence, the choice of ligand is pivotal to the success of the catalyst.



Scheme 5.2

It is thought that the complexation of the chiral amino alcohol ligand to the metal results in the formation of a single diastereomer of Ru-H. A preference has also been noted for the α-conformation in which the carbinol carbon is below the plane of the ring and so is closer to the hydride (see figure 5.2) than in the β-conformation (carbinol carbon above plane of the ring and on the opposite face to hydride).

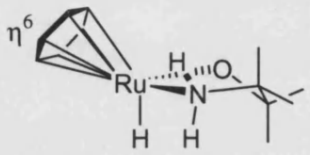


Figure 5.2 Ruthenium hydride complex in the α-conformation

In the transition state the calculations show that the over-riding determinant of the preferred conformation is not the orientation of the carbinol carbon, but rather the H-N-Ru-H dihedral angle (θ_D). The TS prefers this 1,4-dipole to be near planar, with a dihedral angle approaching zero. The conformation of the complexed ligand in the transition state can therefore change from that of the Ru-H intermediate to allow for increased planarity. With ethanolamine however, Andersson found that the Ru-H TS also adopts the α-conformation to reduce the dihedral angle to -10° (figure 5.3).

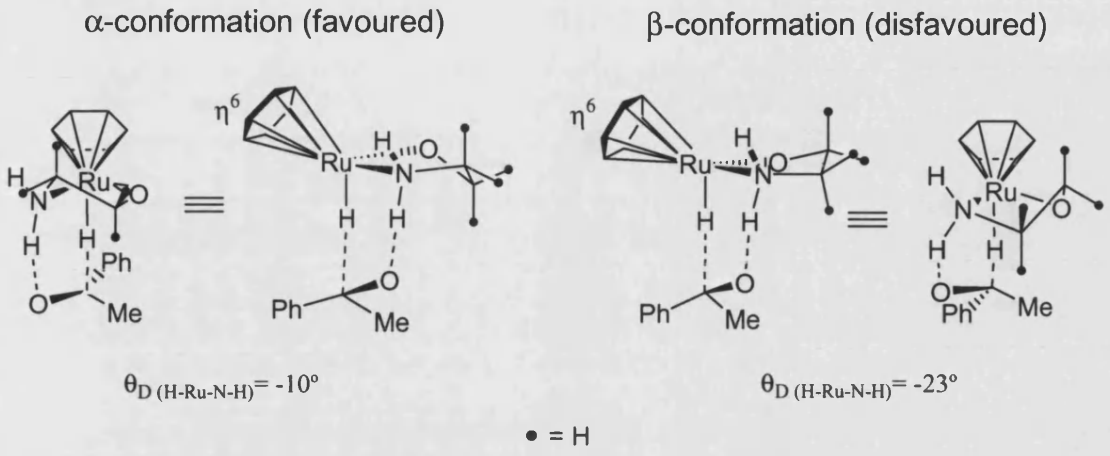


Figure 5.3 Calculated transition state for an ethanolamine-Ru-H complex

5.2.2 Enantioselectivity

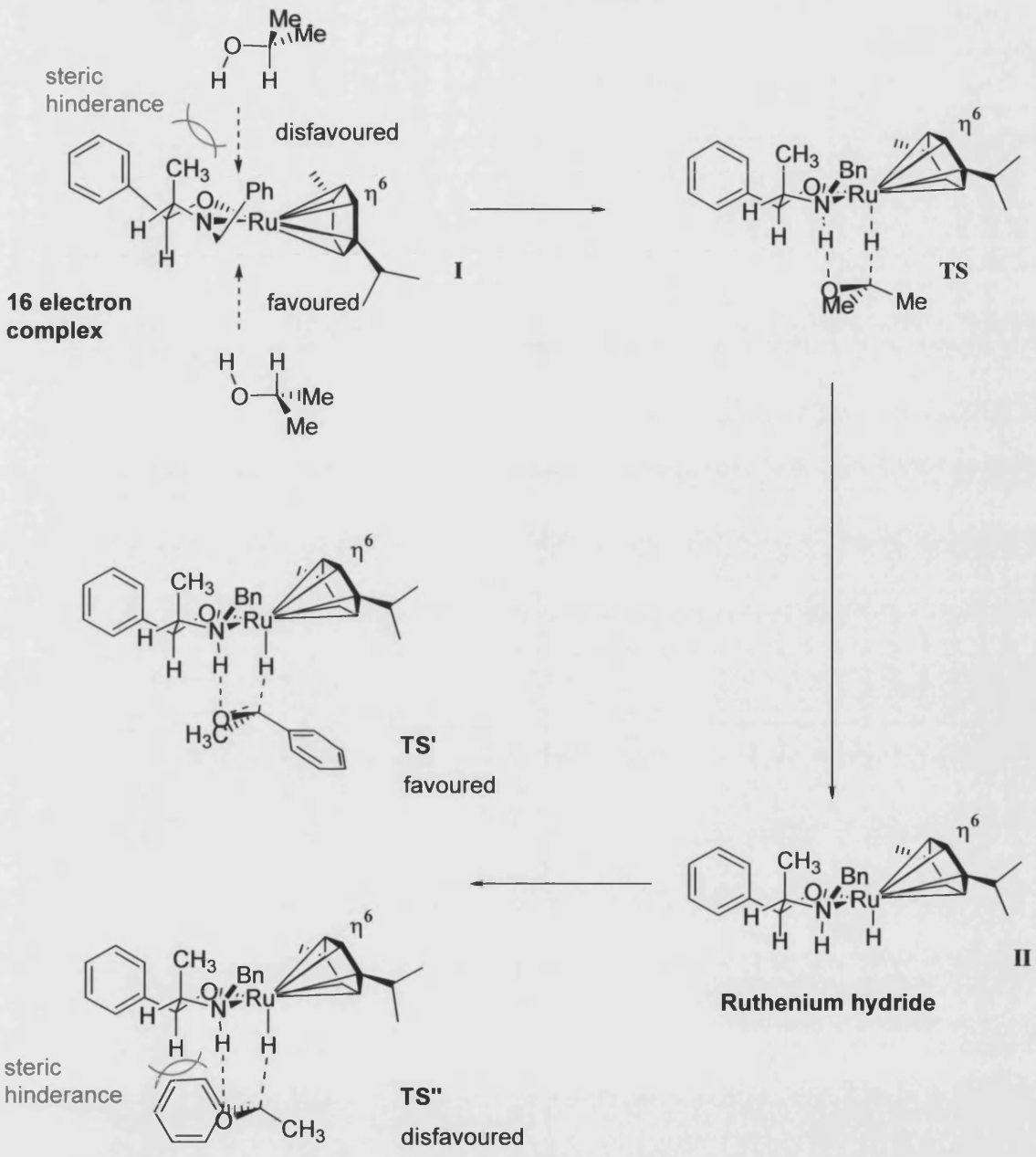
Though many chiral ligands have been developed for the reaction there is still no completely satisfactory rationale for the observed enantio-induction in pro-chiral ketones such as acetophenone. The problem is that the observed chiral induction does not fit with any steric repulsion argument between substituents on the chiral ligand and those on the substrate. Instead, it is argued that chiral induction is caused by the geometry of the fully assembled 5-membered metal chelate ring and that this is governed by the structure of the chiral ligand. The chirality transfer may then be aided by a CH-π interaction between the arene ligand on the Ru complex and the aromatic group on the hydrogenation substrate (e.g. phenyl group on acetophenone).

5.3 LIGAND OPTIMISATION

5.3.1 Rationale for observed selectivity

In the course of this investigation, we discovered a very effective amino alcohol ligand scaffold. *N*-Benzyl substituted norephedrine **98** had, in conjunction with a Ru(II) complex, resulted in a highly reactive and selective catalyst capable of giving (*R*)-1-phenylethanol in 91% ee at 28°C.

We believe that the Ru hydride complex with *N*-benzyl-(1*R*,2*S*)-norephedrine forms exclusively the (*S*)-α 5-membered ring diastereomer **II** (see scheme 5.3). This diastereomer would be expected to have an α-conformation because this allows the phenyl group on the carbinol carbon to orient itself in an equatorial position. The smaller *syn*-methyl group on the carbon adjacent to the nitrogen must then occupy an axial position to minimise repulsive steric interactions with the equatorial phenyl group. We believe that the methyl group plays a major part in ensuring the diastereoselectivity of the formation of ruthenium hydride. Approach of isopropanol from the upper face of **I** is prohibited by steric crowding against the methyl (and, to a lesser extent, the phenyl) group which points upwards. The less crowded lower face is therefore much preferred and complexation of isopropanol from this face gives the proposed (*S*)-α-**98**-Ru-H diastereomer (**II**).



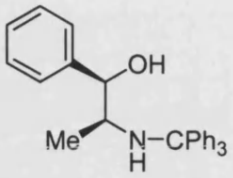
Scheme 5.3 Rationale for the exclusive formation of (*S*)-α-**98**-Ru-H

In the ruthenium hydride **II**, the axial methyl group also forces the *N*-alkyl group equatorial which in turn forces the NH proton to become axial and the N-H bond to point into the same plane as the Ru-H, thus minimising the H-Ru-N-H dihedral angle in **TS'**.

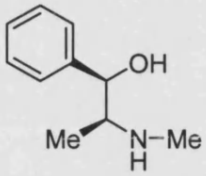
These factors give ruthenium hydride **II** a favourable geometry for the complexation of a ketone. The **TS'** (scheme 5.3) leads to formation of (*R*)-1-phenylethanol. We believe this enantioselectivity may be partly due to a 1,3-interaction between the axial proton on the carbinol carbon and the substituents of the incoming ketone. The lowest energy transition state **TS'** has acetophenone exposing its pro-*R* face to the metal hydride, so that the smaller methyl substituent of the ketone points toward the carbinol proton. The pro-*S* alignment would push the larger phenyl group toward the proton increasing the energy of **TS''**. The selectivity may also be due to favourable interactions between the phenyl group of the substrate and the aryl group on the metal, as well as to the benzyl group, but these are discussed later.

5.3.2 The importance of the *N*-benzyl moiety

We wanted to investigate whether the enhancement in selectivity of *N*-benzyl norephedrine (**98**) over norephedrine was due to the specific properties of the *N*-benzyl group or whether the introduction of any group with some degree of steric bulk on the amine terminus would result in a similar degree of enantioselectivity.

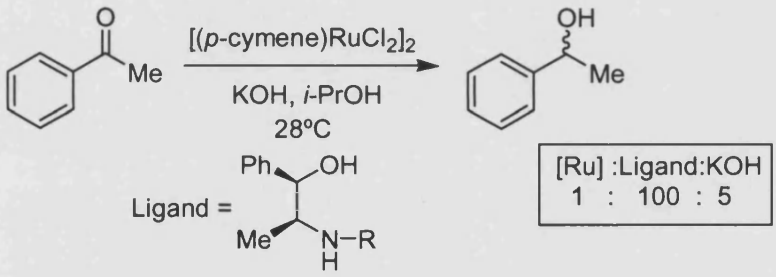


100



101

We prepared *N*-trityl-norephedrine (**100**) and screened both this ligand and (1*R*,2*S*)-(-)-ephedrine (**101**) in the transfer hydrogenation of acetophenone at 28°C (see table 5.2).

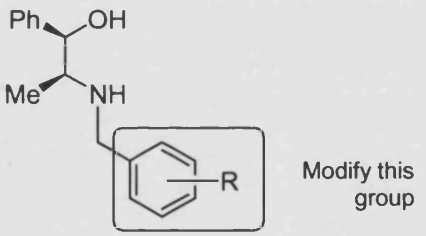


R	Ligand	% conversion	% ee (config.)	Time / hours
	**98**	95	91 (*R*)	2
	**99**	92	92 (*R*)	3
-CPh_3	**100**	95	81 (*R*)	1
-Me	**101**[60]	96	88 (*R*)	1

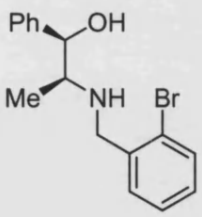
Table 5.2

The enantioselectivities obtained from *N*-trityl **100** and *N*-methyl **101** were lower than those obtained for *N*-benzyl **98** and *N*-methylthiophenyl **99**. The results indicated that the choice of R group on the amine terminus was important in optimising the enantioselectivity of the catalyst but that simply increasing the size of this group was not a clear determinant of enantioselectivity.

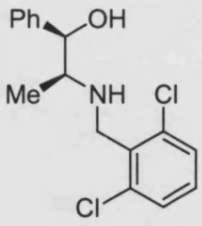
Having found that *N*-benzyl norephedrine ligands were more effective than their methyl or trityl analogues, we wanted to investigate what effect, if any, alteration of its steric properties would have on the selectivity of the catalyst. Thus, further derivatives were prepared (scheme 5.4).



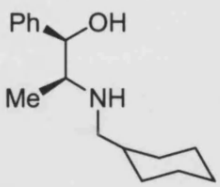
Ligands Prepared;



102



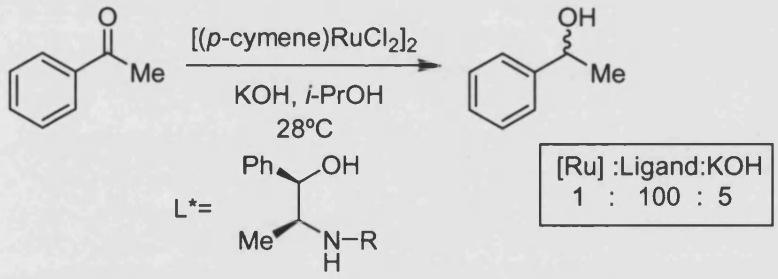
103



104

Scheme 5.4

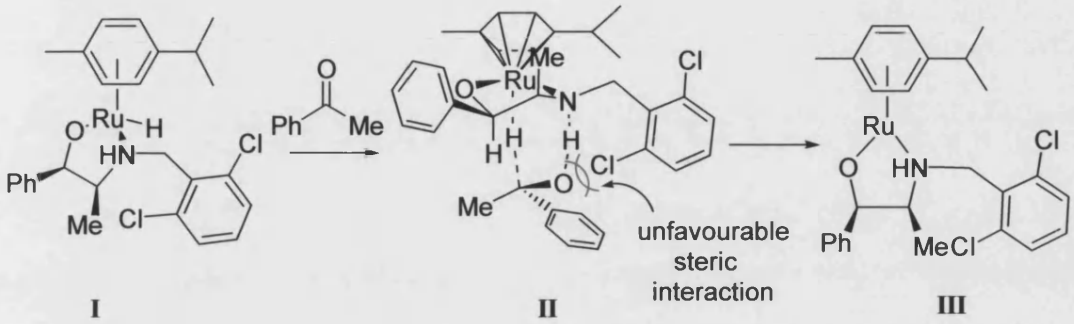
In **102** and **103** the size of the flat phenyl group is increased to a more bulky *ortho*-substituted benzene. With **104**, the phenyl ring was converted to a cyclohexyl unit which is no longer flat. The ligands would also have slightly different electronic properties, having a small effect on the basicity of the amine. These three ligands were tested in the transfer hydrogenation of acetophenone. The results, summarised in table 5.3, show a fall in the ee's obtained from both **102** and **103** when compared to *N*-benzyl norephedrine **98**, while *N*-cyclohexylmethyl **104** gave similar selectivities but with a slower reaction. Though 2-bromophenyl **102** still delivered a reasonably high conversion with an ee of 88% (*R*), the reaction was much slower than with **98**. 2,6-Dichlorophenyl **103** displayed much reduced activity, with the reactions only proceeding with low conversions and a very low ee of 22%.



R group	Ligand	% conversion	% ee (config.)	Time / hrs
2-Br-Ph-CH_2-	**102**	83	88 (*R*)	18
2,6-Cl_2-Ph-CH_2-	**103**	23	23 (*R*)	19
cyclohexyl-CH_2-	**104**	94	93 (*R*)	16
Ph-CH_2-	**98**	95	91 (R)	2

Table 5.3

We believe that these observations are largely due to increased steric crowding as the size of the R group increases from phenyl towards 2,6-dichlorophenyl (scheme 5.5).



Scheme 5.5 Possible reasoning for poor activity of ligand **103**

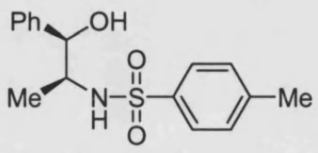
It is believed that the catalytic cycle involves the formation of a ruthenium hydride **I**. Transition state **II** would experience significant steric repulsion between the *ortho*-chlorine atoms of the benzyl group and the reacting ketone. This would cause its formation to be less favourable than the corresponding intermediate with **98** (R=$PhCH_2$) making this catalyst less reactive.

N-Cyclohexylmethyl derivative **104** provides a larger group than *N*-benzyl **98**, but it has less potential for steric crowding than 2,6-dichlorophenyl **103** due to the absence of *ortho*-substituents pointing into the reaction pocket. While the observed effects are most likely due to steric factors, the introduction of a cyclohexyl group would also make the NH slightly more electron rich, potentially having an electronic effect on catalyst activity (whereas **102** and **103** are relatively electron withdrawing). The initial results from **104** were encouraging, with the ligand achieving both a high conversion and

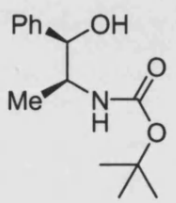
enantioselectivity at 28°C. The reaction was somewhat slower than the corresponding reaction with the *N*-benzyl ligand **98**.

5.3.3 Electronic effects of the nitrogen R-group

Though we believe that the lower catalytic activity of ligands **102** & **103** in comparison to **98** is predominantly due to the steric factors described above, an electronic effect could not be ruled out as a contributing cause of lower reactivity. It is notable that the least reactive analogue (**103**) is also that with the most electron withdrawing substituent on the amine terminus and that, conversely **98**, the most active ligand, has a relatively electron donating R-group. The explanation solely in terms of steric crowding also seems inconsistent with the *N*-trityl analogue **100** which was more reactive than *N*-benzyl **98** even though it has a larger R-group (though lacking *ortho*-substituents). To the best of our knowledge, no study has discussed the electronic effects of amine substituents on amino alcohol catalysts. To investigate whether electron withdrawing groups might in fact reduce catalyst reactivity we prepared *N*-tosyl (**105**) and *N*-Boc (**106**) norephedrine. Both groups are electron withdrawing, with large Hammett σ-coefficients.



105



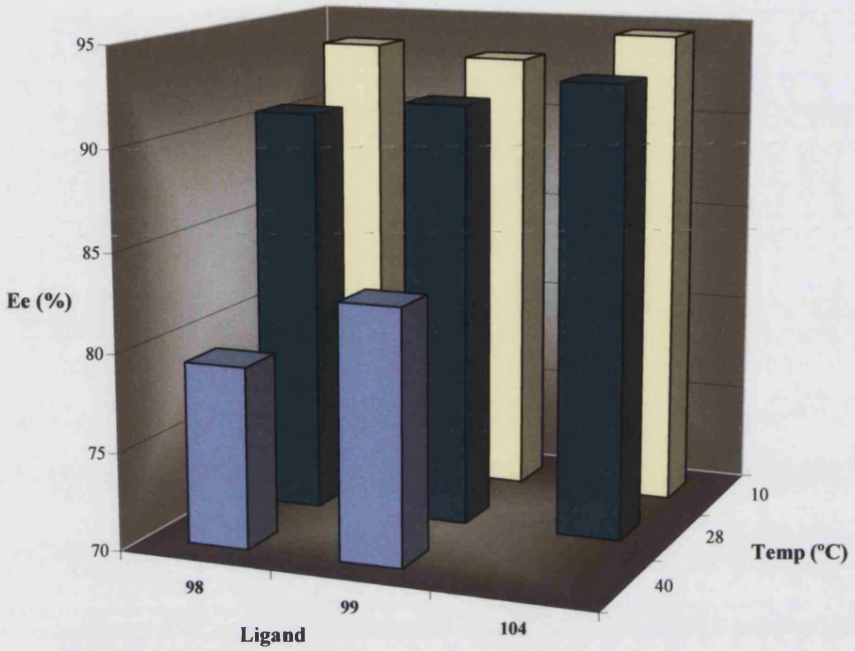
106

These ligands were then tested in the ruthenium catalysed transfer hydrogenation of acetophenone, at 40°C, in which neither gave any significant conversion. These results indicate that electronic properties of the amine substituent may play an important role in determining the activity of the catalyst. This observed effect might be due to the resulting change to the polarisation of the Ru-N bond with changing electronic properties of the R-group. The Ru-N 16-electron complex relies on a high degree of bond polarisation with a substantial fractional charge on the nitrogen, to initiate the dehydrogenation of isopropanol. With electron withdrawing R-groups, such as tosyl or Boc, the polarisation of this bond is somewhat decreased with a concomitant reduction in dehydrogenative activity. This results in slower or negligible formation of the Ru-H catalyst and hence slower reaction rates.

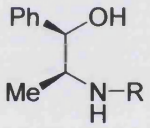
5.3.4 Effect of lowering reaction temperature

The effect of lowering reaction temperature on the selectivity of these catalysts in the reduction of acetophenone was investigated and the results are shown in table 5.4.

The thiophene ligand **99** showed a noticeable increase in ee from 82% to 93% on reducing the reaction temperature from 40°C to 28°C. However, the ee did not increase any further upon reducing the temperature to 10°C. The reactivity dropped substantially at this temperature with the reaction achieving a conversion of only 32% using 5 mol% Ru.



Ligand =



R	Ligand	10°C		28°C		40°C	
		% conv	% ee	% conv	% ee	% conv	% ee
	**98**	82	93	95	91	93	79
	**99**	32	93	92	92	97	83
	**104**	87	95	94	93	n.d.	

Table 5.4 Results from transfer hydrogenation of acetophenone with varying temperature

The pattern was similar with *N*-benzyl ligand **98** where the reduction in temperature caused a noticeable increase in selectivity but a concomitant decrease in activity. However, the catalyst was still active at 10°C, with the reaction going to 82% conversion within 4 hours. The ee's increased from 83% at 40°C to 94% at 10°C. This reactivity pattern mirrors that of the imino alcohol ligands where the presence of the thiophenyl moiety led to a decrease in activity compared to phenyl. This gives further evidence that the sulphur atom of the thiophene may be interacting with the Ru centre, having a detrimental effect on activity. However, this interaction is probably a weak one and hence the catalyst remains active. The results also show that there is no overall gain in selectivity in having a thiophenyl moiety on the ligand with both ligands **98** and **99** giving near identical selectivities.

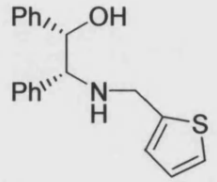
Ligand **104** again showed only a slight increase in selectivity (94 to 95% ee) upon reducing the temperature from 28°C to 10°C but the selectivities with this ligand were slightly higher than with the other two analogues.

It therefore seemed that reactions run at 28°C provided an optimal balance between activity and enantioselectivity.

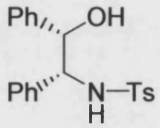
5.4 ATTEMPTED OPTIMISATION OF THE AMINO ALCOHOL BACKBONE

The most effective ligands prepared had all been based around (1*R*,2*S*)-norephedrine. To investigate whether ligands based around (1*S*,2*R*)(+)-2-amino-1,2-diphenylethanol, a ligand with a complementary geometry, could

provide higher selectivities than *N*-benzyl norephedrine ligands, we prepared **107** and **108**. However, when tested in the transfer hydrogenation of acetophenone at 40°C, neither ligand gave any significant conversion. This observation was consistent with previous findings showing that this ligand backbone was ineffective[53].



107



108

We believe that analogues of (1*S*,2*R*)(+)-2-amino-1,2-diphenylethanol cannot form active catalysts because of the requirement for an axial phenyl group (see figure 5.5). This requirement would probably make the 5-membered metallocycle highly unstable and may even prohibit its formation. Even if the Ru-H complex were to form, there may be significant steric repulsions between the axial phenyl group and both the aryl group on Ru and the CH_2 of the *N*-benzyl group.

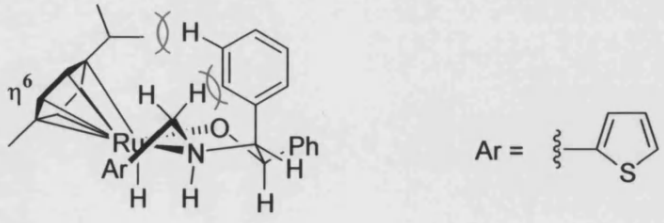
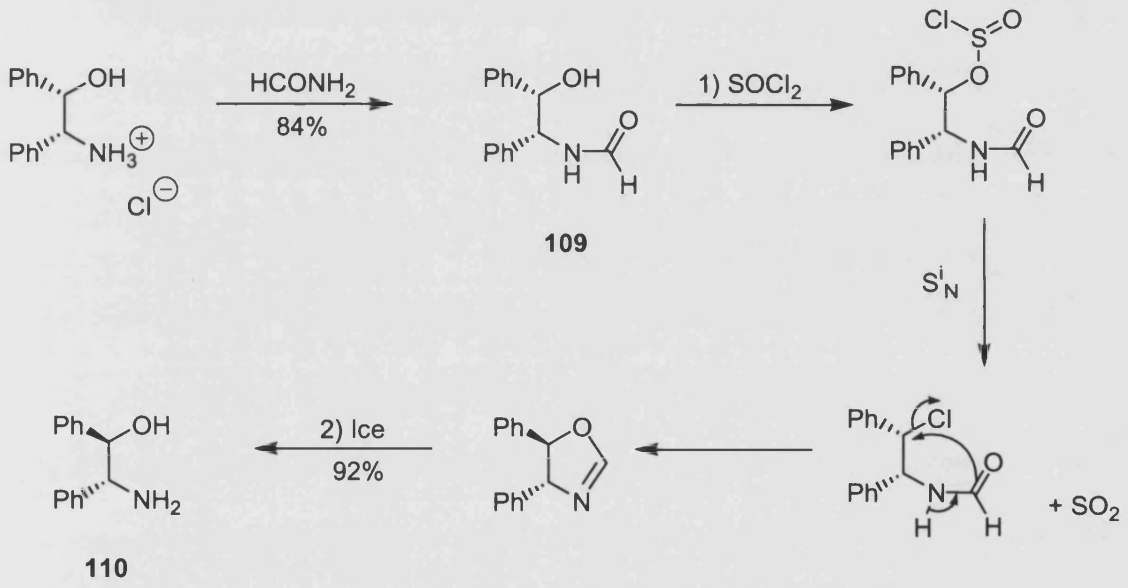


Figure 5.5 Proposed rationale for failure of ligand **107**

We then wished to investigate whether a 1,2-anti-β-amino alcohol ligand might be more effective in the reaction. An attempt was made to convert (1*R*,2*S*)-norephedrine to (1*S*,2*S*)-norephedrine by treatment with HCl, using a procedure developed by Fodor *et al.*[61], but the attempt was unsuccessful with the product obtained not being enantiomerically pure.

We therefore prepared (1*R*,2*R*)(+)-2-amino-1,2-diphenylethanol (**110**), a ligand known to be effective[53], using the procedure given in scheme 5.6.

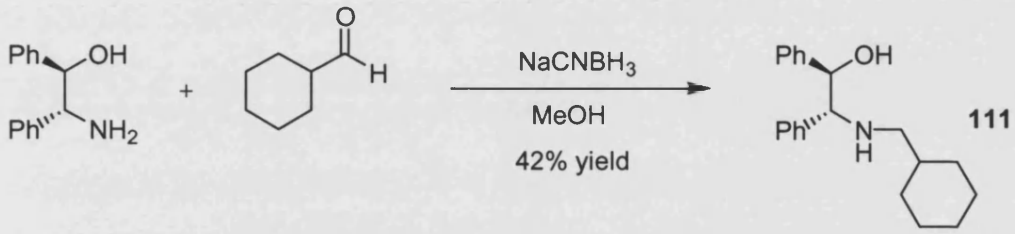


Scheme 5.6

The key step in the synthesis, developed by Weijlard *et al.*[62], is the inversion of the alcohol group of *N*-formyl-2-amino-1,2-diphenylethanol (**109**) using thionyl chloride. The reaction mechanism, shown in scheme 5.6, proceeds via formation of an oxazoline intermediate which is then hydrolysed to give **110**.

The product was obtained in high overall yield and possessed an optical rotation in line with the literature value.

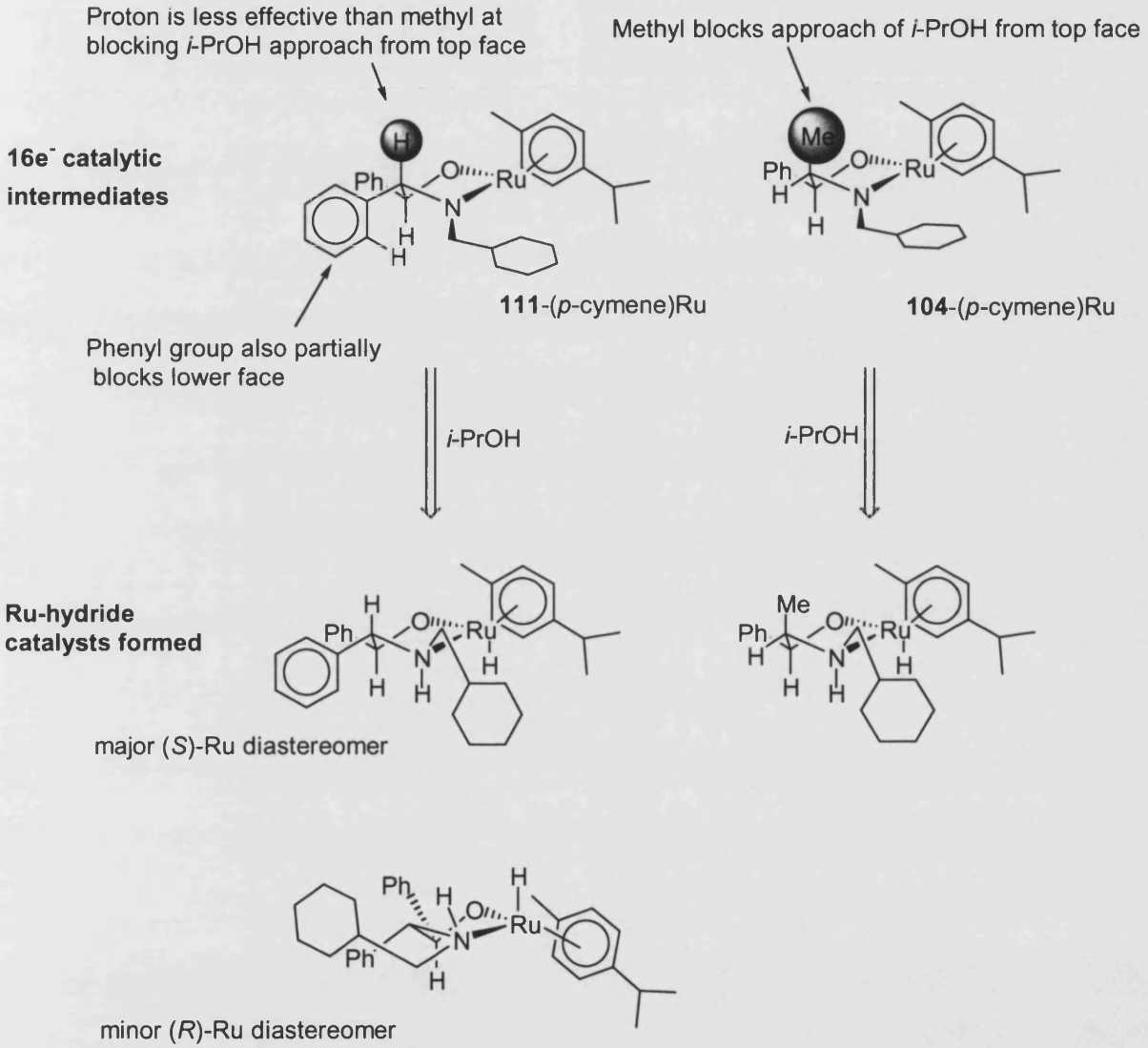
Ligand **111** was prepared by reductive amination of cyclohexane carboxaldehyde with **110** using $NaCNBH_3$ (see scheme 5.7).



Scheme 5.7

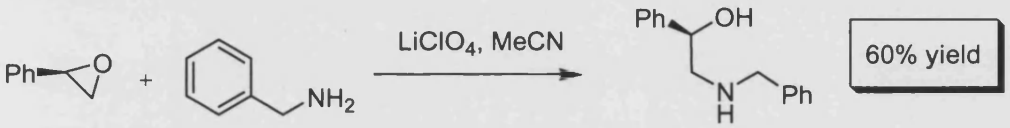
The ligand was moderately active in the reduction of acetophenone, the reaction going to 92% conversion within 20 hours at 28°C, but the enantioselectivity was lower than that obtained with **104** at only 76% ee (*R*). We believe that this lower enantioselectivity may be caused by the **111**-(*p*-cymene)Ru intermediate (see scheme 5.8). Unlike *N*-cyclohexylmethyl norephedrine **104**, which has a methyl group pointing axially up from the plane of the ring, ligand **111** only possesses an axial proton. Furthermore, its equatorial phenyl group on the amino carbon may partially obstruct the lower face. This reduces the difference in steric crowding between the two ring faces of the $16e^-$ intermediate. Therefore hydrogen delivery from isopropanol may occur on either the upper or lower face. The minor (*R*)-diastereomer may be selective for the pro-*S* face of acetophenone, so making the reaction less enantioselective. However, the (*R*)-Ru-diastereomer is probably less active

than the (*S*)-diastereomer, due to its higher H-N-Ru-H dihedral angle and so the majority of the reaction probably goes through the (*S*)-Ru-diastereomer.



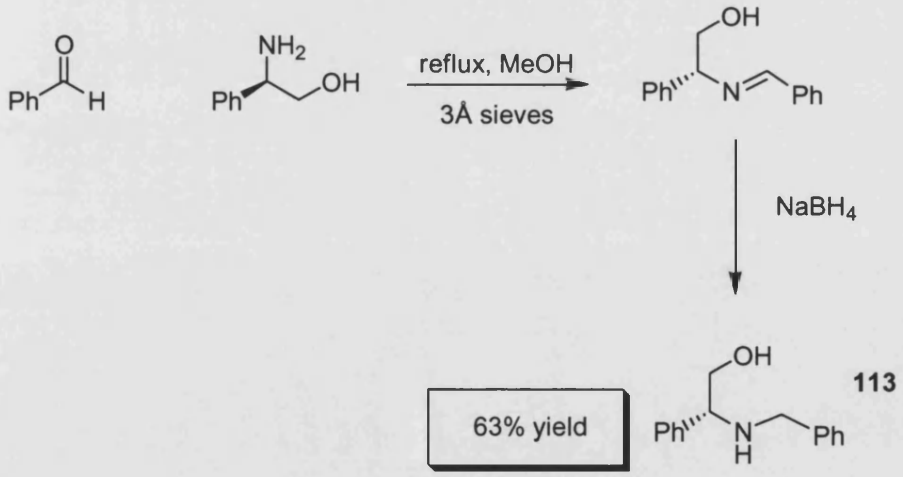
Scheme 5.8 Proposed rationale for lower selectivity of ligand **111** compared to **104**

We then investigated what effect the substitution pattern of the amino alcohol backbone has on the selectivity of these *N*-benzyl amino alcohol catalysts. We wished to see whether a substituent on the carbinol carbon would have a larger effect on enantioselectivity than a substituent on the amino carbon. This in turn could provide further information as to the nature of the catalyst structure as well as an insight into where ligand improvements could be made. To investigate this we prepared ligands **112** and **113** (schemes 5.9 & 5.10).



112

Scheme 5.9



113

Scheme 5.10

Ligand **112** was prepared by opening (*R*)-(+)-styrene oxide with benzylamine while **113** was prepared in two steps by formation of the imine with subsequent reduction using sodium borohydride. The ligands were then tested in the transfer hydrogenation of acetophenone and the results are summarised in table 5.5.

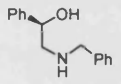
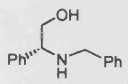
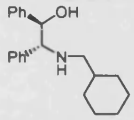
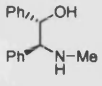
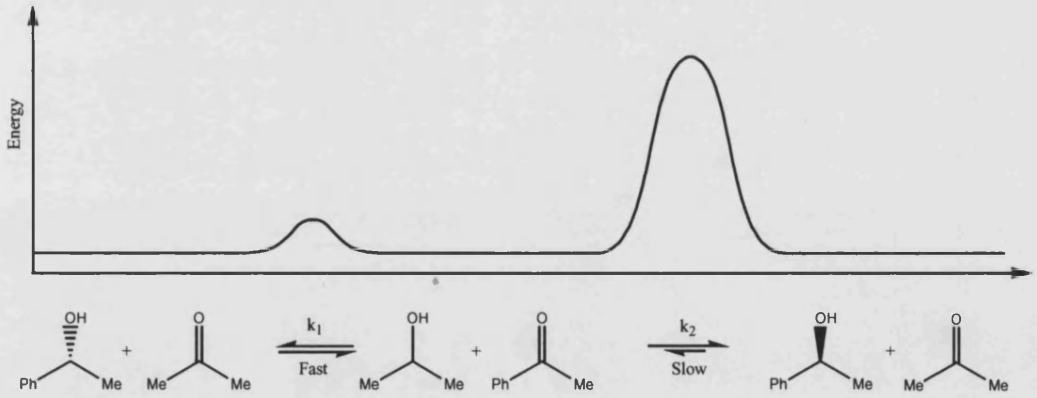
Structure	Ligand	% Conversion	% ee (config.)	Time (hrs)
	**112**	96	76% (*R*)	2
	**113**	86	24% (*R*)	20
	**111**	92	76% (*R*)	20
	**110**	96	33% (*R*)	2
	**114**	97[53]	59% (*S*)	1

Table 5.5 Results from transfer hydrogenation of acetophenone using $[Ru(p\text{-cymene})Cl_2]_2$ at 28°C

Both ligands **112** and **113** proved active in the reaction but differed in their selectivities. Ligand **112** provided (*R*)-1-phenylethanol in substantially higher enantiomeric purity than **113**, suggesting that the substituent on the carbinol carbon of the amino alcohol is more effective in controlling enantioselectivity than the substituent on the amine carbon. Notably **111**, which has a phenyl group on both positions, delivers an ee of 76% (*R*) that is identical to that

obtained from **112** (substituent only on carbinol carbon), but the reaction is much slower. This indicates that the equatorial substituent on the amine carbon hinders the approach of the substrates somewhat.

Ligand **112** showed a marked fall off in ee over time, with the ee falling to 50% (*R*) after 22 hours of reaction. Though the amine carbon substituent does not have a large effect on the selectivity of the catalyst, it does slow the transfer hydrogenation reaction down. As a consequence of microscopic reversibility the more active a catalyst is in the reduction direction, the faster it is in the reverse process. Further, if the catalyst predominantly gives the (*R*)-alcohol then the reverse process with that same catalyst will selectively dehydrogenate the (*R*)-alcohol back to the ketone faster than the (*S*)-alcohol. What should be remembered when designing a catalyst for transfer hydrogenation of ketones under these conditions is that the reaction is effectively a kinetic resolution driven forward by the large excess of isopropanol (see scheme 5.11).



Scheme 5.11

Since the reactants (isopropanol and ketone) are so similar to the products (acetone and secondary alcohol) the transfer hydrogenation reaction is reversible. However, the products are separated long before the competing reversible reactions (k_1 and k_2) have time to reach equilibrium. But if the favoured branch (k_1) equilibrates rapidly, then there will always be a low concentration of ketone present that can be slowly bled off into the undesired enantiomer over elongated time frames.

If the activation energy of the forward reaction is increased (i.e. the reaction is slowed down) this would also slow the rate of back reaction (k_2). So a catalyst could be found where the rate of the forward reaction was still fast enough to be practical, but the back reaction was sufficiently slow so as to allow elongated reaction times without significant loss of ee. The *N*-benzyl norephedrine catalysts developed within this project exhibit this optimal property (see section 5.6).

These results also showed the *N*-benzyl group playing a significant role in the catalyst's ability to differentiate between the opposing pro-chiral faces of the ketone. Amino alcohol ligands without a substituent on nitrogen lead to poor enantioselectivities. However, the *N*-benzyl group gives even higher enantioselection than other groups such as methyl (*c.f.* table 5.5, entries for **111** and **114**) or trityl (*c.f.* table 5.2 entries for **98** & **100**). An alkyl group at this position should help to increase reactivity, because its preference for an equatorial orientation forces the NH proton into an axial orientation (see sect. 5.3.1). However, the increased ability of *N*-benzyl ligands to differentiate between the opposite pro-chiral faces of acetophenone is believed to be due to

a favourable π-stacking interaction between the phenyl groups of the *N*-benzyl moiety and that of the acetophenone substrate (figure 5.6). This re-enforces the effect of the favourable CH/π interactions, proposed by Noyori,[57] between the substrate and the Ru aryl ligand (e.g. *p*-cymene).

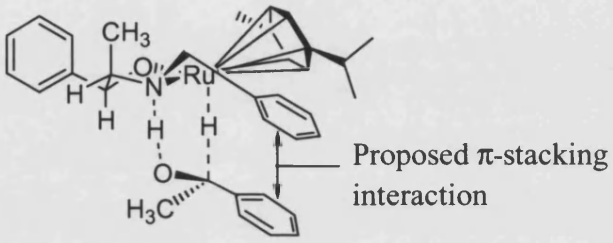


Figure 5.6 Proposed favourable stacking interaction in the TS for ligand **98**

With ligands **104** & **111**, possessing *N*-cyclohexylmethyl groups, there may be a favourable Van der Waals ring-stacking interaction between the cyclohexyl ring and phenyl ring of acetophenone. In theory, the *N*-benzyl ligands should therefore promote higher selectivities across a broad range of aryl-alkyl ketones.

5.5 OPTIMISATION OF THE METAL COMPLEX

It has been shown that modifications to the arene group on the Ru complex can affect the enantioselectivity obtained from the catalyst.[53] In particular, Noyori showed that the selectivity obtained when the aryl group is hexamethylbenzene is greater than when it is benzene. To investigate whether ligands **104** and **111** could deliver higher enantioselectivities, hexamethylbenzene ruthenium chloride dimer was prepared by reacting $[(p\text{-cymene})RuCl_2]_2$ with excess hexamethylbenzene. The two ligands were then tested in the transfer hydrogenation of acetophenone at 28°C using 1 mol% Ru and the results are summarised in table 5.6.

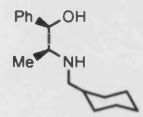
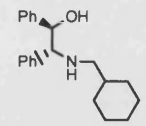
Structure	Ligand	Metal	% Conversion	% ee (config.)
	**104**	$[(C_6Me_6)RuCl_2]_2$	44	93 (*R*)
	104	$[(p\text{-cymene})RuCl_2]_2$	94	93 (*R*)
	**111**	$[(C_6Me_6)RuCl_2]_2$	18	84 (*R*)
	111	$[(p\text{-cymene})RuCl_2]_2$	92	76 (*R*)

Table 5.6 Results from the reduction of acetophenone with varying Ru-Aryl

The selectivities were broadly in line with or slightly above those obtained with $[(p\text{-cymene})RuCl_2]_2$, but the reactions were noticeably slower and did not go to

completion. It is known that reactions using this Ru catalyst are slower, due to the effect of the increased size of the aryl group.

The results from changing $[Ru(p\text{-cymene})Cl_2]_2$ for $[Ir(COD)Cl]_2$ showed a similar pattern to that with imino alcohol ligands (table 4.2), with significantly lower enantioselectivities observed for the reduction of acetophenone. Table 5.7 shows the results obtained after 22 hours at 40°C using 5 mol% of Ir. Though active, it appears that these amino alcohol based ligands are not ideally suited to $[Ir(COD)Cl]_2$.

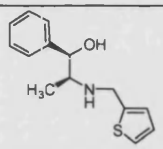
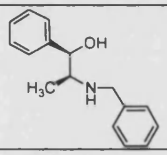
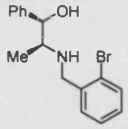
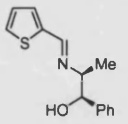
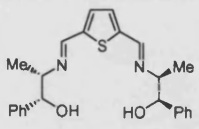
Structure	Ligand	% Conversion	% ee (config.)
	**99**	74	21 (*R*)
	**98**	74	26 (*R*)
	**102**	97	19 (*R*)
	**91**	96	26 (*R*)
	**94**	96	25 (*R*)

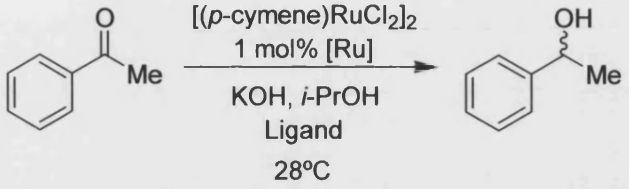
Table 5.7 Results from transfer hydrogenation of acetophenone at 40°C using $[Ir(COD)Cl]_2$

5.6 INVESTIGATION OF CATALYST ACTIVITY

The relative rates of catalysis in the reduction of acetophenone using the most successful ligands developed during this work were investigated. The reactions were monitored over the course of the first hour of reaction, by removing aliquots at time intervals, quenching the reaction by the addition of ether and elution through a pad of flash silica to remove any catalyst present. The aliquots were then analysed by chiral GC to obtain both conversion and ee data. The results are summarised in table 5.8 and graphically in charts 5.1 and 5.2. Ligand **98** was the most active of the *N*-benzyl ligands developed, with an average turnover frequency (TOF) of 126 turnovers/hour over the first 30 minutes of reaction. This was over twice the rate observed for ligands **99** and **111**, while the *N*-trityl ligand **(100)** was the most active however with an average TOF of 300 turnovers/hour.

Chart 5.2 shows that the ee's remained near constant over the reaction period. Interestingly, the ee's do not fall significantly over extended periods with these *N*-benzyl ligands, with **99** for example, giving 1-phenylethanol in 92% ee after 70 hours, the same as it was after 2 hours. This suggests a near negligible rate of back reaction.

The rate of reaction on reducing temperature drops quite dramatically with ligand **104** giving a conversion of only 35% after 1 hour at 10°C compared to a conversion of 72% after 1 hour at 28°C. However, the reaction does proceed towards completion over a prolonged period, showing a 91% conversion after 5 hours.



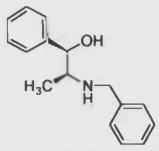
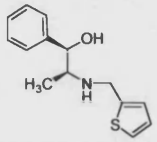
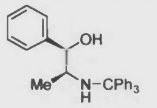
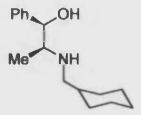
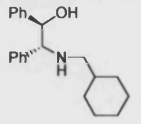
Structure	Ligand	Conversion (%) (after 60 mins)	TOF (turnovers/hr)	ee (%) (after 60 mins)
 ×	**98**	88	126	92
 △	**99**	41	54	91
 □	**100**	95	300	80
 ◆	**104**	72	90	94
 ▣	**111**	50	54	76

Table 5.8

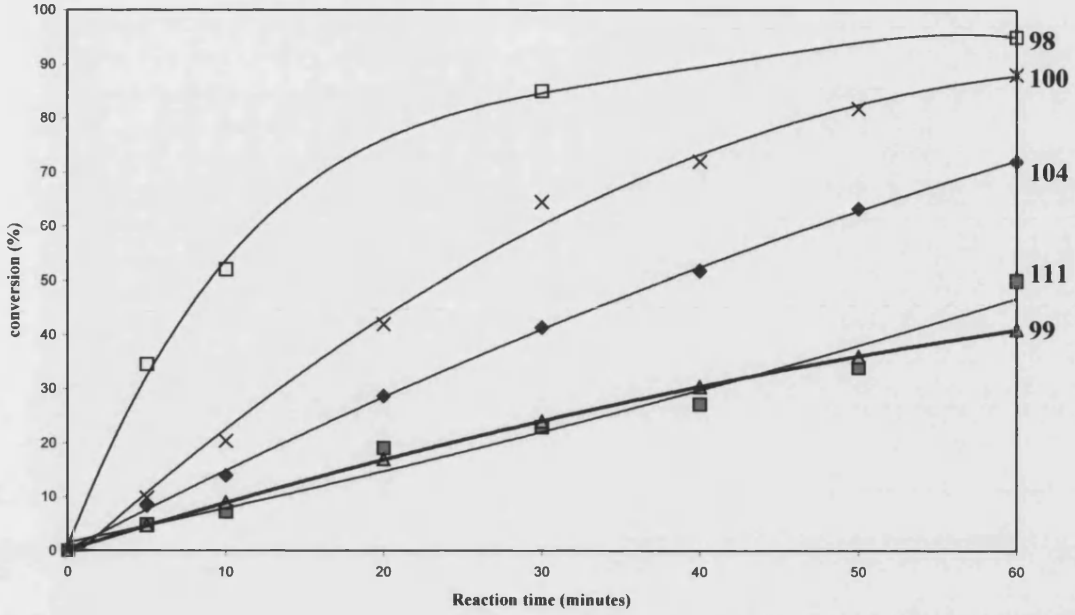


Chart 5.1

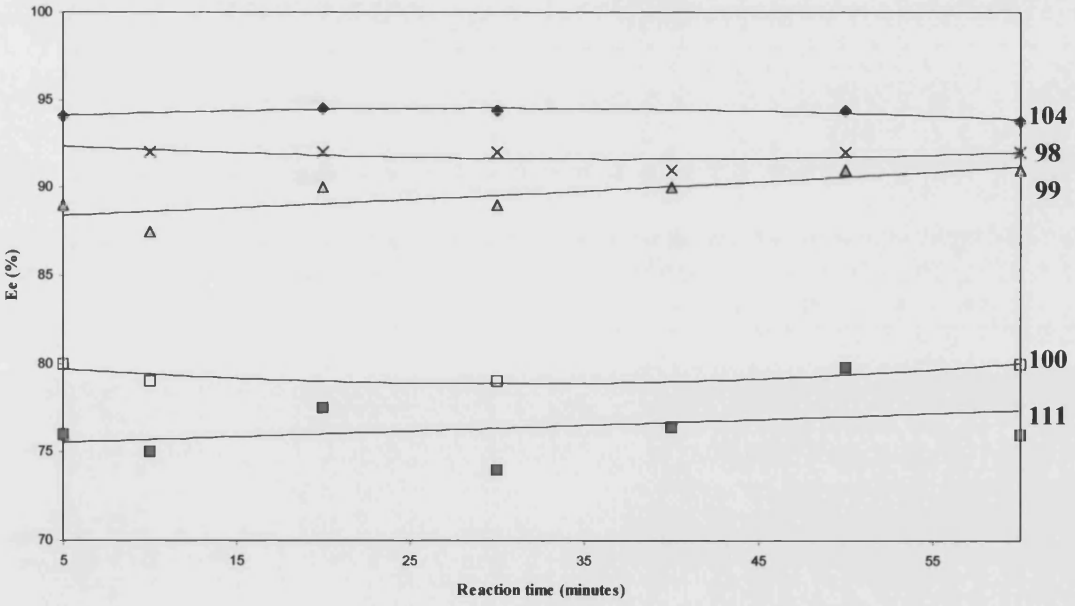


Chart 5.2

5.7 TRANSFER HYDROGENATION ACROSS KETONES

Of the ligands developed, **98**, **99** and **104** delivered the highest selectivities in the reduction of acetophenone with $[(p\text{-cymene})RuCl_2]_2$. The generality of these catalysts in terms of both activity and selectivity was investigated by reducing a number of alternative aryl ketones to their corresponding alcohols. For this purpose, three other ketones were used, namely 4-methoxyacetophenone, 4-bromoacetophenone and 2-acetonaphthone. 4-Methoxyacetophenone is a relatively electron rich ketone which would presumably be less active than 4-bromoacetophenone, having an electron withdrawing substituent. 2-Acetonaphthone is sterically different from acetophenone and would give some indication of the generality of the catalyst's selectivity. The reactions were run at 28°C using $[(p\text{-cymene})RuCl_2]_2$ at a 1 mol% loading of Ru and the results are summarised in table 5.9.

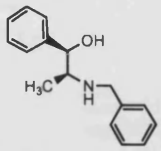
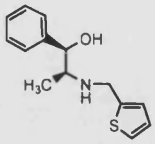
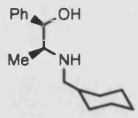
	Ligands		
	98 	**99** 	**104** 
Ketone	**% conv (% ee)**	**% conv (% ee)**	**% conv (% ee)**
acetophenone	95 (91)	92 (92)	94 (93)
4-methoxyacetophenone	55 (89)	n.d.	72 (87)
4-Br acetophenone	>99 (86)	98 (81)	99 (86)
2-acetonaphthone	94 (78)	87 (86)	96 (87)

Table 5.9 Results from the reduction of a number of ketones

High enantioselectivities were obtained with all the ketones investigated with all three ligands, though the highest ee's were observed for the reduction of acetophenone.

5.8 CONCLUSIONS

During the course of this study, a number of enantiopure ligands have been developed for the transfer hydrogenation of pro-chiral ketones. Of these, a new class of amino alcohol ligand, capable of producing alcohols with very high enantiomeric excesses, has been found. These *N*-alkylated, particularly *N*-benzyl, amino alcohols are competitive in terms of enantioselectivity with the best ligands currently known in literature.

We have highlighted a number of properties we believe are important to an amino alcohol ligand, to enable high selectivity. In particular we have shown the importance of the group attached to the carbinol carbon, the nitrogen bound group and the arene ligand. An opportunity exists to prepare ligands, which further explore these areas in order to obtain a more highly selective catalyst. The effect of changing the *N*-benzyl group is especially interesting. Perhaps such groups (e.g. $-CH_2$-naphthyl, $-CH_2$-anthracene) can be selected to maximise favourable π-interactions, allowing one to match a particular ligand to a given class of substrates, leading to even higher ee's.

CHAPTER 6

EXPERIMENTAL SECTION

6.1 INTRODUCTION

In this chapter a summary of the preparative chemistry performed and the analytical data for the products are presented. These products are organised into 4 sections. Section 6.3 concerns the aryl diamine ligands prepared in chapter 2 via the Pd catalysed amination reaction. Section 6.4 lists the ligands prepared in chapter 3. Section 6.5 lists the imine ligands listed in chapter 4 while the amino alcohols of chapter 5 are described in section 6.6. Section 6.7 lists general experimental details for the transfer hydrogenation reaction.

6.2 EXPERIMENTAL MEMORANDA

Spectroscopy

NMR experiments

All NMR experiments were carried out on either the Jeol EX 270, Jeol JMX 400MHz or Varian Gemini 400MHz machines. All chemical shifts, δ, are given in parts per million (ppm) and coupling constants, *J*, given in Hertz.

The following abbreviations are used in the assignments of the NMR spectra;

s - singlet

d - doublet

dd - double doublet

ddd - double double doublet

dt - double triplet

q - quartet

m - multiplet

br. - broad

sex - sextet

In ^{13}C-spectra non-CH peaks are defined as CH_3, CH_2 or ipso, where data was available.

Mass Spectroscopy

Carried out by the University of Bath Mass Spectroscopy service using a Kratos MS 80 Mass Spectrometer.

IR spectroscopy

Carried out using a Perkin Elmer 1600 Fourier transform IR spectrometer.

Optical Rotation

Obtained using an Optical Activity AA-10-automatic polarimeter

Melting Points

Obtained using either a Buchi 535 melting point apparatus and all melting points were uncorrected.

Chromatography

Flash Chromatography

Performed using Merck 60 mesh silica gel.

Chiral HPLC

Carried out using a Thermo Separation Products-Spectraseries UV 100 machine. Chiral columns used were manufactured by Daicel Chemical Industries and were either the Chiracel OD or OJ columns.

Chiral GC

Carried out using a CE Instruments HRGC 8000 series machine in conjunction with a Supelco β-Dex 120 column or a Restek RT-βDEXse^{TM} column.

Materials used

Dry solvents

Dichloromethane and acetonitrile were dried over calcium hydride. Tetrahydrofuran was dried over sodium wire. Isopropanol was dried over 3Å molecular sieves and degassed prior to use.

Metal complexes

Ruthenium and palladium complexes were either bought from Aldrich or kindly donated by Johnson Matthey. All other metal complexes were dontated by Johnson Matthey.

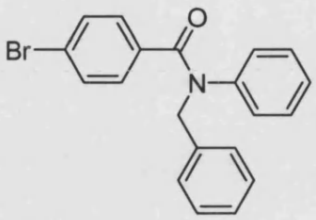
Compound Index

(1*R*,2*R*)-1-*N*-(2-Nitrophenyl)cyclohexane-1,2-diamine	**62**	166
(1*R*,2*R*)-1-*N*-(2,4-Dinitrophenyl)1,2-diaminocyclohexane	**63**	167
(1*R*,2*R*)-1-*N*-(2-Anilino)1,2-diaminocyclohexane	**64**	168
(1*R*,2*S*)-2-*N*-(2-Nitrophenyl)-1-phenyl-2-aminopropanol	**115**	169
(1*R*,2*S*)-2-*N*-(2-Anilino)-1-phenyl-2-aminopropanol	**65**	170
(2*S*)-2-*N*-(2-Nitrophenyl)-3-phenyl-2-aminopropanol	**116**	171
(2*S*)-2-*N*-(2-Anilino)-3-phenyl-2-aminopropanol	**66**	172
(1*S*)-(2-Nitrophenoxy)-1-*N*-(4-toluenesulfonyl)-1-phenylaminoethane	**117**	172
(1*S*)-2-(2-Aminophenoxy)-1-*N*-(4-toluenesulfonyl)-1-phenylaminoethane	**68**	174
(2*S*)-1-(2-Nitrophenoxy)-2-*N*-(4-toluenesulfonyl)-3-phenyl-2-aminopropane	**118**	175
(2*S*)-1-(2-Aminophenoxy)-2-*N*-(4-toluenesulfonyl)-3-phenyl-2-aminopropane	**69**	176
(1*R*,2*S*)-1-(2-Nitrophenoxy)-1-phenyl-2-*N*-(4-toluenesulfonyl)-2-aminopropane	**119**	177
(1*R*,2*S*)-1-(2-Aminophenoxy)-1-phenyl-2-*N*-(4-toluenesulfonyl)-2-aminopropane	**70**	178
(*R*)-2-Phenyl-2-*N*-(5-chloro-2,4-dinitrophenyl)-2-aminoethanol	**72**	179
2,4-*N*-Bis[(*R*)-2-Hydroxy-1-phenylethyl]-1,5-dinitro-2,4-diaminobenzene	**73**	179
(1*R*,2*S*)-1-Phenyl-2-*N*-(5-chloro-2,4-dinitrophenyl)-2-amino propan-1-ol	**74**	180
2,4-*N*-Bis-[(1R,2S)-1-Hydroxy-1-phenyl-prop-2-yl]-1,5-dinitro-2,4-diaminobenzene	**75**	181
2,4-*N*-Bis[(*R*)-2-Hydroxy-1-benzylethyl]-1,5-dinitro-2,4-diaminobenzene	**76**	182
(*R*)-1-*N*-(5-Chloro-2,4dinitrophenyl)-1-cyclohexyl-1-aminoethane	**77**	183
Thiophene-2-carboxaldehyde-(*R*)-1-cyclohexylethyl imine	**86**	185

(*S*)-1-[(2,5-Dimethylimino)thiophene]-1-phenylethane	**87**	186
Thiophene-2-carboxaldehyde-(*S*)-(2-hydroxy-1-phenylethyl)imine	**88**	186
Thiophene-2-carboxaldehyde-(*S*)-(1-hydroxy-3-phenylprop-2-yl)imine	**89**	187
Thiophene-2,5-dicarboxaldehyde-bis[(*S*)-1-hydroxy-3-phenylprop-2-yl]imine	**90**	188
Thiophene-2-carboxaldehyde-[(1*R*,2*S*)-1-hydroxy-1-phenylprop2-yl]imine	**91**	189
Thiophene-2-carboxaldehyde[(*S*)-1-hydroxy-3methylbut-2-yl]imine	**92**	190
Thiophene-2,5-dicarboxaldehyde-bis[(*S*)-1-hydroxy-3-methylbut-2-yl]imine	**93**	191
Thiophene-2,5-dicarboxaldehyde-bis[(1*R*,2*S*)-1-hydroxy-1-phenylprop-2-yl]imine	**94**	192
2-Hydroxybenzaldehyde[(1*R*,2*S*)-1-hydroxy-1-phenylprop-2-yl]imine	**95**	192
Pyrrole-2-carboxaldehyde [(1*R*,2*S*)-1-hydroxy-1-phenylprop-2-yl]imine	**96**	193
(1*R*, 2*S*)-*N*-Benzyl-2-amino-1-phenylpropan-1-ol	**98**	195
(1*R*,2*S*)-1-Phenyl-2-*N*-(2-thiophenylmethyl)amino propan-1-ol	**99**	196
(1*R*,2*S*)-*N*-Trityl-2-amino-1-phenylpropan-1-ol	**100**	197
(1*R*,2*S*)-*N*-(2-Bromobenzyl)-2-amino-1-phenylpropan-1-ol	**102**	198
(1*R*,2*S*)-*N*-(2,6-Dichlorobenzyl)-2-amino-1-phenyl propan-1-ol	**103**	199
(1*R*,2*S*)-*N*-(Cyclohexylmethyl)-2-amino-1-phenyl propan-1-ol	**104**	200
(1*R*,2*S*)-*N*-(4-Toluenesulphonyl)-2-amino-1-phenyl propan-1-ol	**105**	201
(1*R*,2*S*)-*N*-*tert*-Butyloxycarbonyl-2-amino-1-phenyl propan-1-ol	**106**	201
(1*R*,2*R*)-*N*-(Cyclohexylmethyl)-2amino-1,2-diphenylethanol	**111**	202
(1*R*)-*N*-Benzyl-2-amino-1-phenylethanol	**112**	204
(*R*)-*N*-Benzyl-2-amino-2-phenylethanol	**113**	205

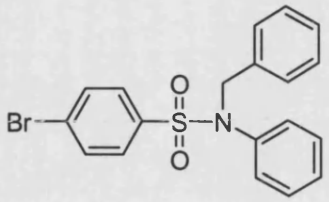
6.3 EXPERIMENTAL FOR CHAPTER 2

N-Benzyl-4-bromo benzoyl anilide (37)



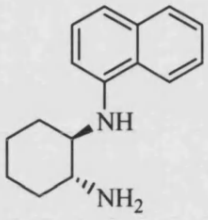
N-Benzylaniline (149mg, 0.81mmol) was taken up in dry DCM (6ml). To the solution was added 4-bromobenzoylchloride (253mg, 1.15mmol) followed by DMAP (99mg, 0.81mmol) and triethylamine (0.46ml, 3.3mmol) and the mixture was then heated at reflux for 2 hours. The crude product was purified by flash chromatography (ethyl acetate-light petroleum, 3:7 v/v) to give a colourless solid (270mg, 91%). Tlc (ethyl acetate - light petroleum, 3:7 v/v) R_f 0.59; m.p. 79-80°C; IR (neat) ν_{max} 1645 (s); δ_H ($CDCl_3$) 5.11 (s, 2**H**), 6.89 (dd, 2**H**, *J* 7.9, 1.8), 7.13 (m, 3**H**), 7.20 (m, 3**H**), 7.28 (m, 6**H**); δ_C ($CDCl_3$) 53.91 (CH_2), 124.15 (ipso), 126.97, 127.47, 127.71, 128.46, 128.49, 129.21, 130.47, 130.96, 134.85 (ipso), 137.28 (ipso), 143.19 (ipso), 169.29 (ipso); HRMS (EI) Found *m/z* 365.0410 (calcd for $BrC_{20}H_{16}NO$ (M^+) 365.0415); Anal. Calcd for $BrC_{20}H_{16}NO$: C, 65.59; H, 4.40; N, 3.82. Found: C, 65.60; H, 4.40; N, 3.97.

***N*-Benzyl-4-bromobenzenesulfanilamide (40)**



N-Phenylbenzylamine (150mg, 0.82mmol) and 4-bromobenzene sulphonyl chloride (296mg, 1.16mmol) were taken up in dry DCM (7ml). To the solution were added triethylamine (0.76ml) then DMAP (98mg, 0.8mmol) and the reaction carried out as in **36** to give, after purification by flash column chromatography (DCM eluent), a colourless crystalline powder (**40**, 325mg, 99%). Tlc (ethyl acetate - light petroleum, 1:9 v/v) R_f 0.46; M.p. 177-178°C; IR (KBr) ν_{max} 1571 (m), 1346 (s), 1158 (s); δ_H ($CDCl_3$) 4.73 (s, 2**H**), 6.97 (m, 2**H**), 7.22 (m, 8**H**), 7.50 (d, 2**H**, *J* 8.6), 7.62 (d, 2**H**, *J* 8.8); δ_C ($CDCl_3$) 54.89 (CH_2), 127.73, 128.08, 128.39, 128.52, 128.92, 129.01, 129.16, 132.16, 138.54 (ipso), 137.63 (ipso), 135.54 (ipso); HRMS (EI) *m/z* 401.0076 (calcd for $BrC_{19}H_{16}NO_2S$ (M^+) 401.0085); Anal. Calcd for $BrC_{19}H_{16}NO_2S$: C, 56.70; H, 4.00; N, 3.48. Found C, 56.30; H, 4.00; N, 3.52.

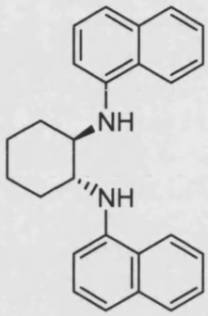
(1*R*,2*R*)-1-*N*-(1-Naphthyl)1,2-diaminocyclohexane (35)



To an oven dried Schlenk tube was added (1*R*,2*R*)-(-)-1,2-diaminocyclohexane (288mg, 2.5mmol), $Pd(DBA)_2$ (29.4mg, 0.05mmol), BINAP (63mg, 0.1mmol) and NaO*t*-Bu (588mg, 4.04mmol). The solids were taken up in dry THF (4ml) and to the solution was added 1-bromonaphthalene (292µl, 2.1mmol). The tube was sealed and the reaction heated at 80°C for 20 hours. The reaction was then diluted with Et_2O, dried over Na_2SO_4 and filtered through celite. Purification by flash silica column chromatography (gradient elution, 100% DCM up to methanol - DCM, 25:75, v/v) gave the product after drying *in vacuo* as an off white solid (120mg, 24%).

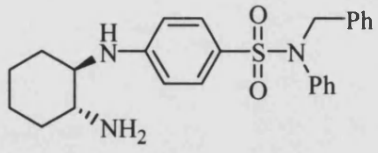
Tlc (methanol-DCM, 2:8 v/v) R_f 0.28; m.p. 101-103°C (decomp); IR (DCM) ν_{maz} 3352, 3304; δ_H ($CDCl_3$) 1.04 (m, 1**H**), 1.31 (m, 3**H**), 1.74 (d, 2**H**, *J* 6.9), 2.01 (dd, 1**H**, *J* 3.1, 5.9), 2.26 (dd, 1**H**, *J* 10.2, 3.1), 2.35 (br s, 2**H**, NH_2), 2.61 (br. s, 1**H**) 3.21 (dt, 1**H**, *J* 10.2, 3.4), 4.20 (br. s, 1**H**, NH), 6.73 (d, 1**H**, *J* 7.8), 7.23 (d, 1**H**, *J* 8.2), 7.32 (t, 1**H**, *J* 8.0), 7.45 (m, 2**H**), 7.78 (dd, 1**H**, *J* 8.2, 1.8), 7.89 (dd, 1**H**, *J* 8.4, 2.0); δ_C ($CDCl_3$) 23.93 (CH_2), 24.77 (CH_2), 30.40 (CH_2), 31.06 (CH_2), 54.10 (CH), 55.33 (CH), 106.17, 117.78, 121.64, 123.91 (ipso), 124.68, 125.94, 126.87, 128.46, 134.41 (ipso), 141.96 (ipso); HRMS (EI) *m/z* 240.1622 (calcd for $C_{16}H_{20}N_2$ 240.1626).

(1*R*,2*R*)-1,2-*N*,*N*-Bis(1-naphthyl)-1,2-diaminocyclohexane (42)



By-product obtained as a colourless powder. IR (KBr) ν_{maz} 3408 (br); δ_H ($CDCl_3$) 1.37 (m, 2**H**), 1.52 (m, 2**H**), 1.86 (m, 2**H**), 2.56 (dd, 2**H**, *J* 2.4, 11.3), 3.63 (m, 2**H**), 4.73 (br s, 2**H**, $N\underline{H}_2$), 6.80 (d, 2**H**, *J* 7.4) 7.27 (m, 4**H**), 7.38 (m, 4**H**), 7.65 (d, 2**H**, *J* 8.6), 7.76 (dd, 2**H**, *J* 0.8, 8.2); δ_C ($CDCl_3$) 24.68 (CH_2), 31.60 (CH_2), 57.95, 120.28, 124.27 (ipso), 124.97, 125.72, 126.05, 128.38, 134.25 (ipso); HRMS (FAB) *m/z* 367.2170 (calcd for $C_{26}H_{27}N_2$ (MH^+) 367.2174).

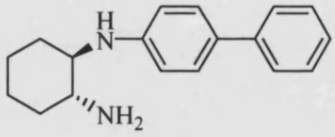
(1*R*,2*R*)-1-*N*[4-(*N*-Benzylsulfanilamido)phenyl]1,2-diaminocyclohexane (41)



To a dry Schlenk tube under argon was added $Pd(DBA)_2$ (17.9mg, 0.028mmol), BINAP (29mg, 0.046mmol) and Cs_2CO_3 (324mg, 0.99mmol). These were taken up in dry THF (4ml) and to the solution was added **40** (250mg, 0.62mmol) and

(1*R*,2*R*)(-)-1,2-diaminocyclohexane (**41**, 99mg, 0.87mmol). The reaction was carried out as in **48** to yield a colourless solid (109mg, 40%). Tlc (methanol - DCM, 2:8 v/v) R_f 0.25; $[\alpha]_D^{20}$ -34.4 (c 0.32, DCM); IR (DCM) ν_{max} 3369, 3253, 3254, 1596, 1340, 1151; δ_H ($CDCl_3$) 1.14 (t, 1**H**, *J* 11.4), 1.29 (m, 3**H**), 1.76 (m, 2**H**), 2.05 (br. m, 4**H**), 2.60 (dt, 1**H**, *J* 6.1, 9.5), 3.09 (m, 1**H**), 4.25 (d, 1**H**, 8.3, NH), 4.69 (s, 2**H**), 6.61 (d, 2**H**, 8.3), 7.03 (ddd, 2**H**, *J* 2.6, 5.1, 7.5), 7.19 (m, 8**H**), 7.40 (d, 2**H**, *J* 8.3); δ_C ($CDCl_3$) 25.04, 25.25, 32.36, 35.19, 54.71, 56.01, 59.24, 112.39, 125.34 (ipso), 127.68, 127.79, 128.54, 128.74, 128.98, 129.21, 130.09, 136.55 (ipso), 139.75 (ipso), 151.93 (ipso); HRMS (EI) *m/z* 435.1981 (calcd for $C_{25}H_{29}N_3O_2S$ (M^+) 435.1980).

(1*R*,2*R*)-1-N-(4-biphenyl)-1,2-diaminocyclohexane (47)

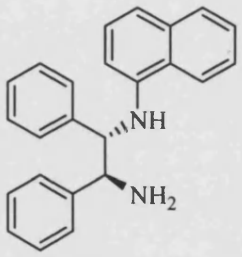


To a dry Schlenk tube under argon was added $Pd(DBA)_2$ (29.4mg, 0.051mmol), BINAP (64mg, 0.10mmol) and NaO*t*-Bu (148mg, 1.54mmol). These were taken up in dry THF (1ml) and to this solution was added 4-bromobiphenyl (200mg, 0.86mmol) and (1*R*,2*R*)(-)-1,2-diaminocyclohexane (133mg, 0.99mmol). The reaction was carried out as in **35** to yield a pale yellow oil (119mg, 52%).

Tlc (methanol-DCM, 3:7 v/v) R_f 0.50; $[\alpha]_D^{30}$ -26.9 (c 0.26, DCM); IR (DCM) ν_{max} 3372.6; δ_H ($CDCl_3$) 0.96 (dd, 1**H**, *J* 12.2, 11.7), 1.27 (m, 4**H**), 1.7 (m, 2**H**),

2.03 (d, 1**H**, *J* 9.5), 2.13 (d, 1**H**, *J* 13.1), 2.48 (m, 1**H**), 3.02 (br s, 3**H**), 3.13 (dt, 1**H**, *J* 10.3, 3.6), 6.76 (d, 2**H**, *J* 8.6), 7.25 (m, 1**H**), 7.37 (t, 2**H**, *J* 7.6), 7.43 (d, 2**H**, *J* 8.5), 7.51 (d, 2**H**, *J* 7.3); δ_C ($CDCl_3$) 24.73 (CH_2), 24.97 (CH_2), 32.07 (CH_2), 33.90 (CH_2), 55.66, 58.66, 113.85, 126.07, 126.16, 127.95, 128.63, 130.36 (ipso), 140.99 (ipso), 147.23 (ipso); HRMS (FAB) *m/z* 267.1857 (calcd for $C_{18}H_{23}N_2$ (MH^+) 267.1862).

(1*S*,2*S*)-*N*-(1-Naphthyl)-1,2-diphenyl-1,2-ethanediamine (48)

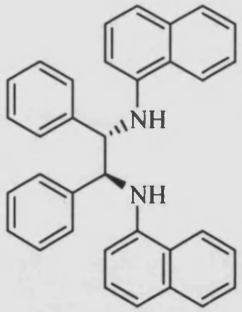


To an oven dried pressure tube cooled under argon was added $PdDBA_2$ (16.5mg, 0.0029mmol), BINAP (35.4mg, 0.0057mmol), and NaO*t*-Bu (89mg, 0.92mmol). These were taken up in dry THF (2ml) and to the suspension was added 1-bromonaphthalene (80µl, 0.58mmol) followed by (1*S*,2*S*)(-)-1,2-diphenylethylenediamine (146mg, 0.69mmol) after which the tube was sealed under argon. The mixture was stirred at 80°C for 6 hours, after which time tlc showed that the reaction was complete. The reaction mixture was taken up in Et_2O (7ml) and the solids removed by filtration through Celite. The crude mixture was purified by flash silica column chromatography (*n*-hexane - EtOAc, 7:3 v/v) to afford a pale yellow oil (122mg, 62%). Tlc (methanol - DCM, 1:9 v/v) R_f 0.53; IR (thin film) ν_{max} 3379

(br, NH_2), 1581, 1524, 1477, 1409; δ_H ($CDCl_3$) 1.79 (br. s, 2**H**, $N\underline{H}_2$), 4.40 (d, 1**H**, *J* 4.3), 4.63 (d, 1**H**, *J* 4.3), 6.15 (dd, 1**H**, *J* 6.2, 2.3), 6.18 (br. s, 1**H**, N<u>H</u>), 7.07 (m, 2**H**), 7.21 (m, 2**H**), 7.26 (d, 2**H**, *J* 8.6), 7.29 (d, 2**H**, *J* 7.0), 7.33 (d, 2**H**, *J* 7.0), 7.42 (m, 2**H**), 7.47, (dd, 1**H**, *J* 8.2, 1.6), 7.49 (dd, 1**H**, *J* 8.2, 1.6), 7.74 (dd, 1**H**, *J* 8.0, 1.0), 8.06 (d, 1**H**, *J* 8.2);

δ_C ($CDCl_3$) 61.48, 63.10, 105.56, 116.51, 120.12, 123.47 (ipso), 124.45, 125.44, 126.40, 126.68, 126.75, 127.15, 127.38, 128.31, 128.44, 134.11 (ipso), 141.08 (ipso), 142.10 (ipso), 142.64 (ipso); HRMS (EI) *m/z* 338.1781 (calcd for $C_{24}H_{22}N_2$ (M^+) 338.1783); Anal. Calcd for $C_{24}H_{22}N_2$: C, 85.17; H, 6.55; N, 8.28. Found C, 84.9; H, 6.68; N, 8.16.

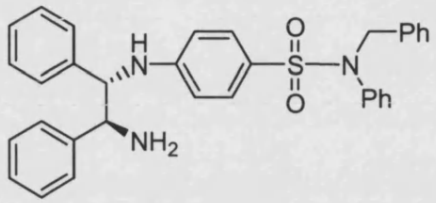
(1*S*,2*S*)-*N*,*N*'-Bis(1-naphthyl)-1,2-diphenyl-1,2-ethanediamine (44)



By-product obtained as a colourless solid.

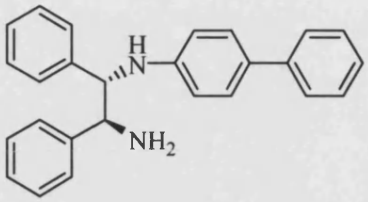
Tlc (ethyl acetate - light petroleum, 2:8 v/v) R_f 0.54; δ_H ($CDCl_3$) 4.94 (s, 2**H**), 5.40 (br. s, 2**H**), 6.38 (dd, 2**H**, *J* 7.4, 7.8), 7.15 (m, 2**H**), 7.21 (d, 2**H**, *J* 7.0), 7.26 (m, 6**H**), 7.34 (m, 4**H**), 7.44 (m, 4**H**), 7.78 (dd, 2**H**, *J* 6.3, 7.0), 7.89 (dd, 2**H**, *J* 6.6, 7.0); HRMS (FAB) *m/z* 465.2332 (calcd for $C_{34}H_{29}N_2$ (MH^+) 465.2331).

(1*S*,2*S*)-1-*N*-[4-{*N*-Benzylsulfanilamido)phenyl]-1,2-diphenyl-1,2-diaminoethane (50)



To a dry Schlenk tube under argon was added $Pd(DBA)_2$ (16.2mg, 0.028mmol), BINAP (33.8mg, 0.054mmol) and NaO*t*-Bu (82mg, 0.85mmol). These were taken up in dry THF (3ml) and to the solution was added *N*-benzyl-4-bromobenzenesulfanilamide (**40**) (200mg, 0.5mmol) and (1*S*,2*S*)(-)-1,2-diphenylethylenediamine (129mg, 0.61mmol). The reaction was carried out as in **48** (see above) to yield a colourless powder (**50**, 224mg, 84%). Tlc (methanol - DCM, 1:9 v/v) R_f 0.53; $[\alpha]_D^{20}$ = +5.4 (c 5.0, DCM); IR (DCM) ν_{max} 3368 (br), 1512, 1343 (s); δ_H ($CDCl_3$) 1.48 (br. s, 2**H,** $N\underline{H}_2$), 4.35 (d, 1**H**, *J* 3.8), 4.51 (dd, 1**H**, *J* 6.1, 4.0), 4.60 (s, 2**H**, $C\underline{H}_2$), 5.89 (d, 1**H**, *J* 6.1, N<u>H</u>), 6.38 (d, 2**H**, *J* 8.8), 6.95 (dd, 2**H**, *J* 7.0, 2.7), 7.12 (m, 4**H**), 7.16 (m, 4**H**), 7.24 (d, 2**H**, *J* 7.2), 7.25 (d, 2**H**, *J* 9.0), 7.33 (m, 8**H**); δ_C ($CDCl_3$) 54.28 (CH_2), 60.75, 62.68, 112.39, 124.83 (ipso), 126.59, 126.66, 127.26, 127.32, 127.55, 128.13, 128.36, 128.44, 128.54, 128.72, 128.83, 129.43, 136.24 (ipso), 139.42 (ipso), 140.36 (ipso), 142.44 (ipso), 150.86 (ipso); HRMS (FAB) *m/z* 534.2212 (calcd for $C_{33}H_{32}N_3O_2S$ (MH^+) 534.2216); Anal. Calcd for $C_{33}H_{31}N_3O_2S$: C, 74.27; H, 5.85; N, 7.87. Found C, 74.10; H, 5.90; N, 7.69.

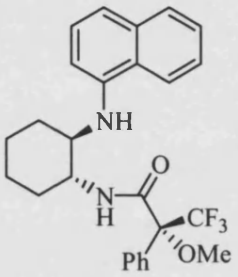
(1*S*,2*S*)-*N*-(4-Biphenyl)-1,2-diphenyl-1,2-ethanediamine (49)



To a dry Schlenk tube under argon was added $Pd(DBA)_2$ (7.8mg, 0.014mmol), BINAP (17.4mg, 0.028mmol) and NaO*t*-Bu (59mg, 0.61mmol). These were taken up in dry THF (1ml) and to the solution was added 4-bromobiphenyl (80mg, 0.34mmol) and (1S,2S)(-)-1,2-diphenylethylenediamine (101mg, 0.48mmol). The reaction was carried out as in **48** to give a pale yellow oil (50mg, 40%). Tlc (methanol - DCM, 1:9 v/v) R_f 0.50; $[\alpha]_D^{25}$ -19 (c 1.0, DCM); IR (DCM) 3372 (m); δ_H ($CDCl_3$) 1.55 (br. s, 2**H**, $N\underline{H}_2$), 4.26 (d, 1**H**, *J* 4.4), 4.43 (d, 1**H**, *J* 4.6), 5.21 (br. s, 1**H**, N<u>H</u>), 6.45 (dd, 2**H**, *J* 2.9, 6.7), 7.24 (m, 15**H**), 7.37 (dd, 2**H**, *J* 1.2, 8.3); δ_C ($CDCl_3$) 61.18, 63.31, 113.62, 125.83, 126.17, 126.72, 126.92, 127.24, 127.44, 127.66, 128.39, 128.51, 128.59, 129.77 (ipso), 141.25 (ipso), 141.53 (ipso), 142.86 (ipso), 146.85 (ipso); HRMS (FAB) *m/z* 365.2027 (calcd for $C_{26}H_{25}N_2$ (MH^+) 365.2018).

Mosher's Amides

(1*R*,2*R*)-1-*N*-[(2*R*)-2-methoxy-2-phenyl-3,3,3-trifluoropropanoyl]-2-*N*-(1-naphthyl)-1,2-diaminocyclohexane (53)



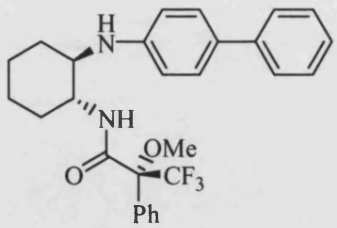
(1*R*,2*R*)-1-*N*-(1-Naphthyl)1,2-diaminocyclohexane (**35**) (43mg, 0.18mmol) was taken up in anhydrous dichloromethane (4ml). To this solution was added (*R*)(-)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (37.6mg, 0.15mmol). The solution was stirred briefly and then 4-dimethylaminopyridine (3.6mg, 0.03mmol) was added followed by triethylamine (31µl, 0.22mmol). The reaction was stirred at room temperature overnight resulting in formation of a single product. The reaction was then washed with water and the aqueous phase back extracted three times with DCM. The combined organic phases were dried over sodium sulphate and purified by flash silica filtration (eluent; light petroleum followed by ethyl acetate-light petroleum, 2:8 v/v). This gave a colourless solid (**53**, 57mg, 83%); Tlc (ethyl acetate - light petroleum, 2:8 v/v) R_f 0.37; IR (neat) ν_{maz} 3406, 1684; δ_F ($CDCl_3$) -69.47; δ_H ($CDCl_3$) 1.26 (m, 1**H**), 1.47 (m, 4**H**), 1.83 (d, 1**H**, *J* 10.9), 1.89 (d, 1**H**, *J* 8.6), 2.16 (m, 1**H**), 2.45 (d, 1**H**, *J* 12.5), 3.17 (s, 3**H**), 3.40 (dt, 1**H**, *J* 3.9,

10.5), 4.13 (m, 1**H**), 6.53 (d, 1**H**, *J* 7.4), 6.61 (t, 2**H**, *J* 7.8), 6.97 (t, 1**H**, *J* 7.6), 7.03 (d, 1**H**, *J* 8.6, NH), 7.15 (d, 2**H**, *J* 7.8), 7.20 (dd, 1**H**, *J* 1.6, 8.2), 7.25 (dd, 1**H**, *J* 1.6, 9.8), 7.31 (d, 1**H**, *J* 7.8), 7.39 (t, 1**H**, *J* 7.4), 7.55 (d, 1**H**, *J* 8.2), 7.76 (d, 1**H**, *J* 8.2); δ_C ($CDCl_3$) includes 24.50 (CH_2), 25.02 (CH_2), 31.30 (CH_2), 32.53 (CH_2), 52.77 (CH_3), 54.74, 59.32, 82.78 (q, *J* 25.3) 120.44, 123.43 (ipso), 125.06, 125.78, 126.00, 127.70, 128.15, 128.97, 131.27 (ipso), 134.36 (ipso). 168.00 (ipso); HRMS (EI) *m/z* 456.2020 (calcd for $C_{26}H_{27}F_3N_2O_2$ (M^+) 456.2024).

Racemic modification

δ_F ($CDCl_3$) -69.11, -69.47.

(2*R*)-*N*-[{(1*R*,2*R*)-2-(1,1'-biphenyl)-4-amino}cyclohexyl]-3,3,3-trifluoro-2-methoxy-2phenylpropanamide (54)



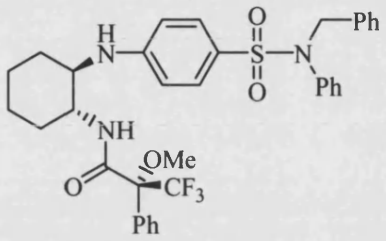
(*R*)(+)-α-methoxy-α-fluoromethylphenyl acetic acid (100mg, 0.43mmol) was taken up in thionyl chloride (0.94ml, 13mmol). To the solution was added catalytic NaCl

(2.5mg) and the mixture was allowed stirred at 90°C for 40 hours by which time complete consumption of the acid had occurred. Thionyl chloride was removed by rotary evaporation and the residue was taken up in dry DCM (3ml). To this was added (1*R*,2*R*)-1-*N*-(4-biphenyl)-1,2-diaminocyclohexane (**47**) (77mg, 0.28mmol), triethylamine (600µl, 4.3mmol, 10eq.) and DMAP (6mg, 0.05mmol). The reaction was stirred at room temperature for one hour. The mixture was then washed with brine solution and back extracted four times with DCM. The combined organic layers were dried over Na_2SO_4 and the solids filtered under suction. The product was then further purified by flash column chromatography (*n*-hexane - ethyl acetate 95:5 v/v) to give a colourless oil (**54**, 22mg, 16%). Tlc (ethyl acetate - hexane, 1:1 v/v) R_f 0.65; IR (neat) ν_{max} 1639; δ_F ($CDCl_3$) -69.21; δ_H ($CDCl_3$) 1.35 (m, 5**H**), 1.79 (d, 2**H**, *J* 12.1), 2.03 (d, 1**H**, *J* 12.5), 2.32 (dd, 1**H**, *J* 3.5, 13.7), 3.21 (dt, 1**H**, *J* 3.5, 10.2), 3.29 (s, 3**H**), 3.90 (dq, 1**H**, 3.7, 10.2), 6.63 (d, 2**H**, *J* 8.6), 7.25 (tt, 1**H**, *J* 1.2, 7.4), 7.41 (dd, 2**H**, *J* 2.0, 8.6), 7.37 (m, 5**H**), 7.52 (m, 4**H**); δ_C ($CDCl_3$) includes 24.44 (CH_2), 24.72 (CH_2), 29.71 (CH_2), 32.29 (CH_2), 52.93, 55.01 (CH_3), 58.16, 126.09, 126.24, 127.44, 128.01, 128.53, 128.65, 129.50, 133.00 (ipso), 141.14 (ipso), 146.88 (ipso), 167.25 (ipso); Tlc (ethyl acetate – *n*-hexane) R_f 0.65; HRMS (FAB) *m/z* 482.2186 (calcd for $C_{28}H_{30}F_3N_2O_2$ (MH^+) 482.2181).

racemic modification

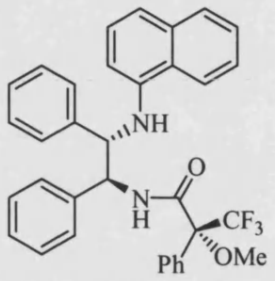
δ_F ($CDCl_3$) -69.40, -68.98

(1*R*,2*R*)-1-*N*-[(2*R*)-2-methoxy-2-phenyl-3,3,3-trifluoropropanoyl]-2-*N*-[4-(benzylsulfanilamido)phenyl]-1,2-diaminocyclohexane (55)



(1*R*,2*R*)-1-*N*-[4-(*N*-Benzylsulfanilamido)phenyl]-1,2-diaminocyclohexane **(41)** (20.3mg, 0.047mmol) and (*R*)(-)-α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride (9.8mg, 0.039mmol) were taken up in anhydrous DCM (3ml). To the solution was added 4-dimethylaminopyridine (1mg, 0.008mmol) and triethylamine (8.2µl, 0.06mmol). The reaction was carried out as for **53** above to give a colourless oil (**55**, 24mg, 95%). Tlc (DCM) R_f 0.47; IR (neat) ν_{maz} 3342, 1684; δ_F ($CDCl_3$) -69.34 (97.5%), -69.95 (2.4%); δ_H ($CDCl_3$) 1.39 (m, 6**H**), 1.83 (d, 1**H**, *J* 9.8), 1.88 (d, 1**H**, *J* 9.0), 2.07 (d, 1**H**, *J* 9.8), 2.26 (d, 1**H**, *J* 12.5), 3.19 (m, 1**H**), 3.24 (d, 3**H**, *J* 0.8), 3.97 (m, 1**H**), 4.69 (d, 1**H**, *J* 14.5), 4.73 (d, 1**H**, *J* 14.4), 6.39 (d, 2**H**, *J* 9.0), 7.04 (m, 1**H**), 7.05 (d, 1**H**, *J* 7.9), 7.05 (d, 1**H**, *J* 8.2), 7.12 (d, 1**H**, *J* 8.2), 7.15 (d, 1**H**, *J* 7.8), 7.23 (m, 10**H**), 7.40 (dd, 2**H**, *J* 2.7, 9.0); δ_C ($CDCl_3$) includes 24.36 (CH_2), 24.93 (CH_2), 32.23 (CH_2), 32.40 (CH_2), 52.40, 54.49 (CH_3), 54.79 (CH_2), 58.97, 77.21, 110.99, 124.53 (ipso), 127.29, 127.34, 127.65, 128.13, 128.33, 128.57, 128.61, 129.48, 129.74, 131.53 (ipso), 136.15 (ipso), 139.40 (ipso), 150.50 (ipso), 167.82 (ipso); HRMS (EI) *m/z* 651.2375 (calcd for $C_{35}H_{36}F_3N_3O_4S$ 651.2378).

(1*S*,2*S*)-1-*N*-[(2*R*)-2-methoxy-2-phenyl-3,3,3-trifluoropropanoyl]-2-*N*-(1-naphthyl)-1,2-diphenylethane 1,2-diamine (56)

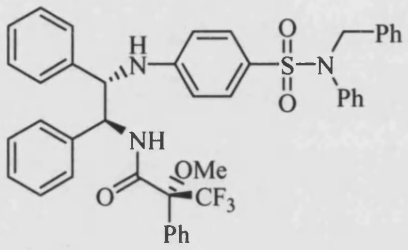


(1*S*,2*S*)-*N*-(1-Naphthyl)-1,2-diphenyl-1,2-ethanediamine (**48**) (34mg, 0.10mmol) and (*R*)(-)-α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride (21.2mg, 0.084mmol) were taken up in anhydrous DCM (2ml). To the solution was added 4-dimethylaminopyridine (2mg, 0.016mmol) and triethylamine (17.6μl, 0.13mmol). The reaction was carried out in similar fashion to **53** to give a colourless solid (**56**, 46mg, 99%). Tlc (ethyl acetate - light petroleum, 2:8 v/v) R_f 0.42; IR (neat) ν_{maz} 3310, 1687; δ_F ($CDCl_3$) -68.875; δ_H ($CDCl_3$) 3.29 (s, 3**H**), 4.87 (d, 1**H**, *J* 8.7), 5.43 (t, 1**H**, *J* 8.2), 6.33 (dd, 1**H**, *J* 0.8, 6.3), 7.06 (m, 2**H**), 7.10 (d, 1**H**), 7.14 (m, 6**H**), 7.25 (dd, 3**H**, *J* 2.7, 6.2), 7.34 (m, 3**H**), 7.41 (d, 2**H**, *J* 8.2), 7.45 (dt, 1**H**, *J* 2.0, 5.1), 7.45 (d, 1**H**, *J* 9.4), 7.56 (d, 1**H**, *J* 7.8), 7.74 (dd, 1**H**, *J* 2.4, 6.9), 7.88 (dd, 1**H**, *J* 2.0, 9.4); δ_C ($CDCl_3$) includes 55.16 (CH_3), 59.50, 63.65, 98.38, 105.73, 117.60, 120.16, 123.47 (ipso), 124.78, 125.60, 126.06, 127.21, 127.30, 127.47, 128.09, 128.19, 128.32, 128.45, 128.58, 129.43, 132.02 (ipso), 134.03 (ipso), 137.53 (ipso), 139.05 (ipso), 141.43 (ipso), 167.12 (ipso); HRMS (EI) *m/z* 554.2195 (calcd for $C_{34}H_{29}F_3N_2O_2$ (M^+) 554.2181).

Racemic modification

δ_F ($CDCl_3$) -68.90, -69.26

(1*S*,2*S*)-1-*N*-[(2*R*)-2-Methoxy-2-phenyl-3,3,3trifluoropropanoyl]-2-*N*-[4-(*N*-benzylsulfanilamido)phenyl]-1,2-diphenyl-1,2-diaminoethane (58)



(*R*)(+)-α-Methoxy-α-trifluoromethylphenylacetic acid (37.9mg, 0.16mmol) was taken up in thionyl chloride (4ml), NaCl (catlaytic) was added and the mixture stirred at reflux for 3 days. The solvent was then evaporated and the mixture taken up in dry DCM (3ml) and to the solution was added (1*R*,2*R*)-1-*N*[4-(*N*-Benzylsulfanilamido)phenyl]1,2-diaminocyclohexane (**41**) (25mg, 0.047mmol), triethylamine (0.23ml) and DMAP (catalytic). The reaction was stirred at room temperature for 1 day, brine was added and the layers extracted with DCM (3x). The combined organic layers were dried over Na_2SO_4 and the crude product purified by flash column chromatography (ethyl acetate - light petroleum, 1:1 v/v) to give the product as a colourless oil (**58**, 8mg, 23%).

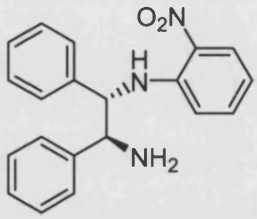
δ_F ($CDCl_3$) -69.20; δ_H ($CDCl_3$) 3.27 (s, 3**H**), 4.63 (s, 1**H**), 4.64 (s, 1**H**), 4.69 (m, 1**H**), 5.34 (dd, 1**H**, *J* 8.5, 9.1), 5.82 (d, 1**H**, *J* 6.2), 6.36 (d, 2**H**, *J* 9.1), 6.97 (m, 2**H**), 7.03 (m, 2**H**), 7.09 (m, 2**H**), 7.16 (m, 10**H**), 7.29 (m, 5**H**), 7.32 (d,

2H, *J* 8.5), 7.40 (t, 1H, *J* 7.3), 7.45 (d, 2H, *J* 7.6), 7.60 (d, 1H, *J* 8.2); δ_C ($CDCl_3$) includes 29.69, 54.46, 54.98, 59.24, 64.76, 77.21, 112.26, 125.86, 127.37, 127.75, 127.83, 128.23, 128.44, 128.57, 128.67, 128.91, 128.99, 129.55, 129.81, 131.90, 136.24, 136.76, 138.72, 139.45, 150.21, 168.39; HRMS (FAB) *m/z* 750.2607 (calcd for $C_{43}H_{39}F_3N_3O_4S$ (MH^+) 750.2614).

6.4 EXPERIMENTAL FOR CHAPTER 3

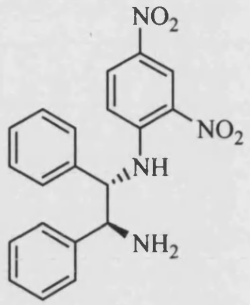
Mono-arylated diamine ligands

(1*S*,2*S*)-*N*-(2-Nitrophenyl)-1,2-diphenyl-1,2-ethanediamine (60)



(1*S*,2*S*)-(-)-DPEN (111mg, 0.52mmol) was taken up in dry acetonitrile (10ml). To the solution was added 2-fluoronitrobenzene (55µl, 0.52mmol) and triethylamine (182µl, 3mmol). The reaction was heated at 80°C for 8 hours, then the solvent was evaporated and the product purified by flash column chromatography (gradient elution; ethyl acetate - *n*-hexane, 1:9 v/v followed by ethyl acetate - *n*-hexane, 2:8 v/v) to afford a yellow oil (**60**, 65mg, 37%). Tlc (ethyl acetate - *n*-hexane, 2:8 v/v) R_f 0.45; $[\alpha]_D^{23}$ -153.0 (c 1.33, $CHCl_3$); IR (neat) ν_{max} 3357, 1618, 1586, 1352; δ_H ($CDCl_3$) 1.60 (br. s, 2**H**, N<u>H</u>$_2$), 4.49 (d, 1**H**, *J* 2.9), 4.68 (dd, 1**H**, *J* 2.9, 6.6), 6.40 (d, 1**H**, *J* 8.8), 6.50 (ddd, 1**H**, *J* 1.1, 7.0, 8.6), 7.12 (ddd, 1**H**, *J* 1.5, 6.8, 8.3), 7.30 (m, 8**H**), 7.50 (d, 2**H**, *J* 7.0), 8.11 (dd, 1**H**, *J* 1.5, 8.6), 9.42 (br. d, 1**H**, *J* 6.2, N<u>H</u>); δ_C ($CDCl_3$) 60.86, 63.31, 115.16, 115.20, 126.59, 126.70, 127.72, 127.82, 128.49, 132.30 (ipso), 135.77, 140.10 (ipso), 142.13 (ipso), 144.60 (ipso); HRMS (FAB) *m/z* 334.1566 (calcd for $C_{20}H_{20}N_3O_2$ (MH^+) 334.1556).

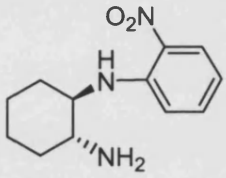
(1*S*,2*S*)-*N*-(2,4-Dinitrophenyl)-1,2-diphenyl-1,2-ethanediamine (61)



2,4-Dinitrofluorobenzene (270mg, 1.45mmol) was taken up in dry DMF (20ml). To the solution was added (1*S*,2*S*)-DPEN (400mg, 1.88mmol). The mixture was stirred briefly before addition of potassium carbonate (241mg, 1.74mmol). The reaction was stirred for 18 hours at room temperature. After this the solvent was evaporated and the solids taken up in ether, filtered through Celite and the filtrate was purified by flash column chromatography (gradient elution; 100% light petroleum to ethyl acetate - light petroleum, 2:8 v/v, in 5% increments) to give the product as a yellow solid after evaporation of the solvent (**61**, 452mg, 82%). Recrystallisation from light petroleum ether - ethyl acetate, 5:1 v/v, gave yellow crystals. Tlc (methanol - DCM, 1:9 v/v) R_f 0.53; $[\alpha]_D^{23}$ +33.8 (c 0.73, $CHCl_3$); IR (KBr) ν_{max} 3383, 3326; δ_H ($CDCl_3$) 1.54 (s, 2**H**, N<u>H</u>$_2$), 4.54 (d, 1**H**, *J* 2.3), 4.73 (dd, 1**H**, *J* 2.3, 6.3), 6.44 (d, 1**H**, *J* 9.4), 7.27 (m, 1**H**), 7.36 (m, 5**H**), 7.43 (dd, 2**H**, *J* 1.2, 8.6), 7.51 (d, 2**H**, *J* 7.0), 7.95 (ddd, 1**H**, *J* 0.8, 2.7, 9.4), 9.08 (d, 1**H**, *J* 2.3), 10.04 (d, 1**H**, *J* 6.2, N<u>H</u>); δ_C ($CDCl_3$) 60.81, 64.16, 115.59, 124.37, 126.50, 126.71, 128.30, 128.64, 129.00, 129.60, 130.09, 131.02 (ipso), 138.88 (ipso), 141.71 (ipso), 147.85 (ipso), 189.70 (ipso); HRMS (FAB) *m/z* 379.1404

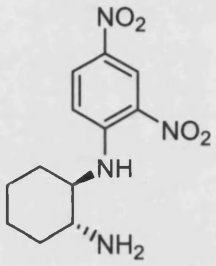
(calcd for $C_{20}H_{19}N_4O_4$ (MH^+) 379.1407); Anal. Calcd for $C_{20}H_{18}N_4O_4$: C, 63.49; H, 4.79; N, 14.81. Found C, 63.5; H, 4.88; N, 14.7.

(1*R*,2*R*)-1-*N*-(2-Nitrophenyl)cyclohexane-1,2-diamine (62)



(1*R*,2*R*)(-)-1,2-Diaminocyclohexane (313mg, 2.74mmol) and 2-fluoronitrobenzene (289ml, 2.74mmol) were taken up in dry MeCN (10ml). Et_3N (0.95ml, 6.82mmol) was added and the reaction was carried out as for **60**. After purification, a yellow powder was obtained (**62**, 467mg, 72%). Tlc (methanol - DCM, 2:8 v/v) R_f 0.48; m.p. 64 °C. $[\alpha]_D^{31}$ -144 (c 0.5, DCM); IR (neat) ν_{max} 3353, 1618, 1572, 1508; δ_H ($CDCl_3$) 1.31 (m, 4**H**), 1.59 (s, 2**H**, $N\underline{H}_2$), 1.78 (m, 2**H**), 2.0 (dd, 1**H**, *J* 4.0, 11.3), 2.10 (dd, *J* 3.1, 10.1), 2.79 (m, 1**H**), 3.31 (dq, 1**H**, *J* 3.9, 9.1), 6.61 (dt, 1**H**, *J*, 1.1, 7.8), 7.01 (d, 1**H**, *J* 8.6), 7.40 (dt, 1**H**, *J* 1.5, 7.8), 8.08 (d, 1**H**, *J* 8.2, NH), 8.15 (dd, 1**H**, *J* 1.5, 8.5); δ_C ($CDCl_3$) 24.56 (CH_2), 24.93 (CH_2), 31.99 (CH_2), 34.71 (CH_2), 55.50, 59.09, 114.43, 115.23, 126.99, 131.91 (ipso), 136.19, 145.68 (ipso); HRMS (FAB) *m/z* 236.1402 (calcd for $C_{12}H_{18}N_3O_2$ (MH^+) 236.1400); Anal. Calcd for $C_{12}H_{17}N_3O_2$: C, 61.20; H, 7.29; N, 17.60. Found C, 61.30; H, 7.30; N, 17.90.

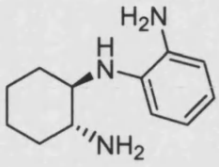
(1*R*,2*R*)-1-*N*-(2,4-Dinitrophenyl)1,2-diaminocyclohexane (63)



To an oven dried flask under N_2 was added (1*R*,2*R*)(-) 1,2-diaminocyclohexane (208mg, 1.82mmol). This was taken up in MeCN (8ml) and to the solution was added 2,4-dinitrofluorobenzene (229µl, 1.82mmol) followed by NaO*t*-Bu (211mg, 2.2mmol). The reaction was stirred at room temperature for 1 hour before being heated to 80°C for a further 2 hours. Tlc analysis showed that the reaction was complete with formation of two products. The mixture was filtered through Celite and then purified by flash column chromatography (gradient elution, 100% DCM followed by MeOH - DCM, 1:9 v/v). This gave the title product as a dark yellow powder (**63**, 186mg, 36%). Tlc (methanol - DCM, 15:85 v/v) R_f 0.48; m.p. 157-158 °C; $[\alpha]_D^{23}$ -73.8 (c 0.52, $CHCl_3$); IR (neat) ν_{max} 3340, 1618, 1591, 1524; δ_H ($CDCl_3$) 1.39 (m, 4**H**), 1.54 (s, 2**H**, N<u>H</u>$_2$), 1.83 (d, 2**H**, *J* 8.3), 2.03 (dd, 1**H**, *J* 9.3, 4.4), 2.13 (dd, 1**H**, *J* 3.9, 11.2), 2.86 (dt, 1**H**, *J* 3.9, 9.6), 3.42 (dq, 1**H**, *J* 3.9, 9.3), 7.12 (d, 1**H**, *J* 9.8), 8.21 (dd, 1**H**, *J* 2.9, 9.8), 8.64 (d, 1**H**, *J* 8.3, N<u>H</u>), 9.10 (d, 1**H**, *J* 2.4); δ_C ($CDCl_3$) 24.33 (CH_2), 24.55 (CH_2), 31.59 (CH_2), 34.97 (CH_2), 55.24, 59.75, 114.62, 124.35, 130.00, 130.11 (ipso), 135.60 (ipso), 148.45 (ipso); HRMS (FAB) *m/z* 281.1253 (calcd for $C_{12}H_{17}N_4O_4$ (MH^+) 281.1250); Anal. Calcd for $C_{12}H_{16}N_4O_4$: C, 51.40; H, 5.75; N, 19.90. Found C, 51.10; H, 5.68; N, 19.60.

Tridentate ligands

(1*R*,2*R*)-1-*N*-(2-Anilino)1,2-diaminocyclohexane (64)

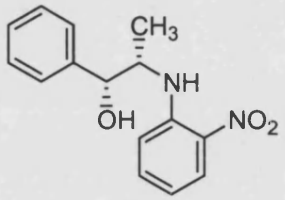


(1*R*,2*R*)-1-*N*-(2-Nitrophenyl)cyclohexane-1,2-diamine (**62**) (354mg, 1.5mmol) and 10% Pd on carbon (35mg) were taken up in ethanol (100ml). The flask was evacuated, flooded with argon 3 times and then flooded with hydrogen. The reaction was stirred at room temperature for 22 hours under a positive pressure of hydrogen and the suspension was then filtered though a pad of Celite. The solvent was evaporated, the crude oil was taken up in DCM, washed with brine solution and the layers separated. The aqueous phase was back extracted (3x) with further DCM. The combined organic phases were dried over Na_2SO_4, and evaporated to dryness under reduced pressure. Attempts to purify the crude product by precipitation of a hydrochloride salt failed, so the residue was purified by running through a short pad of silica (gradient elution; 100% DCM to methanol - DCM, 4:6 v/v). This gave after evaporation of solvent a cream coloured solid (**64**, 285mg, 93%).

Tlc (methanol: DCM, 6:4 v/v) R_f 0.23; m.p. 77-78°C; $[\alpha]_D^{24}$ -153.5 (c 0.99, $CHCl_3$); IR (DCM) ν_{max} 3337; δ_H ($CDCl_3$) 1.03 (ddd, 1**H**, *J* 3.1, 10.9, 12.9) 1.28 (m, 3**H**), 1.73 (m, 2**H**), 1.99 (m, 1**H**), 2.18 (m, 1**H**), 2.57 (ddd, 1**H**, *J* 3.9, 9.8, 10.5), 2.90 (ddd, 1**H**, *J* 3.9, 9.8, 10.9), 6.73 (m, 4**H**); δ_C ($CDCl_3$)

24.99 (CH_2), 25.07 (CH_2), 32.06 (CH_2), 35.29 (CH_2), 55.61, 59.57, 113.59, 116.70, 118.83, 120.17, 135.08 (ipso), 136.71 (ipso); HRMS (EI) *m/z* 205.1573 (calcd for $C_{12}H_{19}N_3$ (M^+) 205.1579).

(1*R*,2*S*)-2-*N*-(2-Nitrophenyl)-1-phenyl-2-aminopropanol (115)

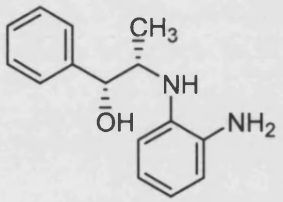


(1*R*,2*S*)-Norephedrine (300mg, 1.98mmol) was taken up in dry THF (8ml). To this was added 2-fluoronitrobenzene (209.2µl, 1.98mmol) and Et_3N (209µl, 1.5mmol). The reaction was heated to 50°C and stirred overnight. The solvent was then evaporated, the crude mixture taken up in DCM and washed with brine. The aqueous phase was back extracted a further three times with DCM. The organic phases were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The product was further purified by flash column chromatography (eluent: DCM) to give a yellow oil (240mg, 44%).

Tlc (DCM) R_f 0.33; $[\alpha]_D^{30}$ +325.6 (c 0.43, DCM); IR (neat) ν_{max} 3583, 3362; δ_H ($CDCl_3$) 1.17 (dd, 3**H**, *J* 6.7, 2.6), 2.61 (br. s, 1**H**), 3.98 (m, 1**H**), 4.94 (br. s, 1**H**), 6.59 (dd, 1**H**, *J* 7.9, 8,5), 6.90 (d, 1**H**, *J* 8.5), 7.29 (m, 1**H**), 7.37 (m, 5**H**), 8.11 (dd, 1**H**, *J* 1.5, 8.6), 8.3 (br. d, 1**H**, *J* 7.9); δ_C ($CDCl_3$) 14.52 (CH_3), 53.47, 75.46, 114.14, 115.23, 126.13, 127.05, 127.93,

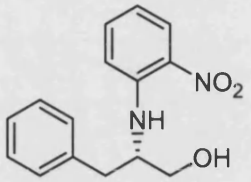
128.49, 131.95, 136.14, 140.67, 144.71; HRMS (FAB) *m/z* 273.1238 (calcd for $C_{15}H_{17}N_2O_3$ (MH^+) 273.1240).

(1*R*,2*S*)-2-*N*-(2-Anilino)-1-phenyl-2-aminopropanol (65)



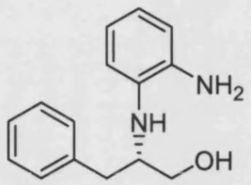
(1*R*,2*S*)-2-*N*-(2-Nitrophenyl)-1-phenyl-2aminopropanol **(114)** (190mg, 0.70mmol) was taken up in absolute ethanol (40ml). To the solution was added 10% Pd on carbon (30mg), the flask was evacuated and flooded with argon three times, and then evacuated and flooded with hydrogen. The reaction was stirred at room temperature under hydrogen for 24 hours. The solids were then filtered off and the solvent evaporated. The crude product was purified by flash column chromatography (gradient elution: DCM followed by methanol - DCM, 5:95 v/v) to give a pale yellow oil (**65**, 176mg, 100%). Tlc (methanol - DCM, 5:95 v/v) R_f 0.46; IR (neat) ν_{max} 3380; δ_H ($CDCl_3$) 1.04 (d, 3**H**, *J* 6.4), 3.32 (br. s, 4**H**), 3.73 (dq, 1**H**, *J* 3.1, 6.7), 4.94 (d, 1**H**, *J* 3.1), 6.72 (dd, 2**H**, *J* 1.2, 4.6), 6.83 (m, 2**H**), 7.27 (m, 1**H**), 7.37 (m, 4**H**); δ_C ($CDCl_3$) 14.31 (CH_3), 54.67, 74.15, 114.29, 117.53, 119.79, 121.04, 126.20, 127.60, 128.55, 135.36 (ipso), 136.27 (ipso), 141.81 (ipso); HRMS (FAB) *m/z* 243.1495 (calcd for $C_{15}H_{19}N_2O$ MH^+ 243.1498).

(2*S*)-2-*N*-(2-Nitrophenyl)-3-phenyl-2-aminopropanol (116)



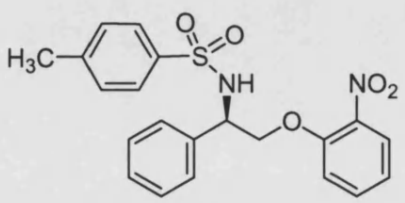
(*S*)-Phenylalaninol (734mg, 4.85mmol) was taken up in dry THF (13ml) and to this was added 2-fluoronitrobenzene (563µl, 5.34mmol) and Et_3N (1.7ml, 12.2mmol). The reaction was stirred at reflux for two days, allowed to cool to room temperature, the solvent evaporated and the crude mixture taken up in DCM. This was washed with brine and the layers separated. The aqueous phase was back extracted a further two times with DCM and the combined organic phases were dried over Na_2SO_4. The solids were filtered and the solvent evaporated to leave a yellow oil. The crude product was purified by flash column chromatography (eluent: ethyl acetate-light petroleum, 3:7 v/v) to give after evaporation of the solvent, an orange oil (721mg, 55%). Tlc (ethyl acetate-light petroleum, 4:6 v/v) R_f 0.31; $[\alpha]_D^{30}$ -426 (c 1, $CHCl_3$); IR (neat) ν_{max} 3362; δ_H ($CDCl_3$) 1.89 (br. s, 1**H**), 2.96 (dd, 1**H**, *J* 6.3, 13.7), 3.04 (dd, 1**H**, *J* 6.4, 13.7), 3.72 (d, 1**H**, *J* 10.7), 3.79 (d, 1**H**, *J* 10.7), 3.98 (m, 1**H**), 6.62 (ddd, 1**H**, *J* 1.0, 6.8, 8.3), 6.89 (d, 1**H**, *J* 8.8), 7.25 (m, 4**H**), 7.38 (ddd, 1**H**, *J* 1.5, 6.8, 8.8), 8.14 (dd, 1**H**, *J* 1.5, 8.8), 8.23 (d, 1**H**, *J* 8.3, N<u>H</u>); δ_C ($CDCl_3$) 37.67 (CH_2), 55.56, 63.42 (CH_2), 114.10, 115.60, 126.83, 127.07, 128.71, 139.28, 132.22 (ipso), 136.19, 137.27 (ipso), 144.95 (ipso).;

(2*S*)-2-*N*-(2-Anilino)-3-phenyl-2-aminopropanol (66)



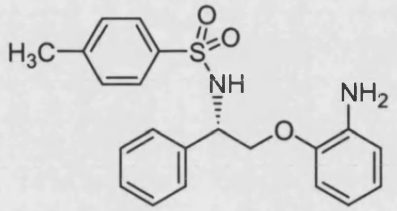
(2*S*)-2-*N*-(2-Nitrophenyl)-3-phenyl-2-aminopropanol (**115**) (617mg, 2.27 mmol) was taken up in ethanol (80ml). 10% Pd on carbon (68mg) was then added. The reaction was carried out as previously to give after purification a colourless solid (**66**, 475mg, 86%). Tlc (methanol - DCM, 1:9 v/v) R_f 0.52; $[\alpha]_D^{23}$ +12.8 (c 0.39, $CHCl_3$); IR (KBr) ν_{max} 3360, 3339; δ_H ($CDCl_3$) 2.83 (dd, 1**H**, *J* 7.6, 13.9), 2.96 (dd, 1**H**, *J* 5.5, 13.7), 3.17 (br. s, 4**H**), 3.50 (dd, 1**H**, *J* 4.7, 10.2), 3.70 (m, 2**H**), 6.72 (m, 2**H**), 6.77 (d, 1**H**, *J* 7.4), 6.84 (m, 1**H**), 7.22 (dd, 2**H**, *J* 1.6, 7.4), 7.25 (dd, 1**H**, *J* 2.0, 7.8), 7.30 (d, 1**H**, *J* 7.4), 7.32 (m, 1**H**); δ_C ($CDCl_3$) 37.98 (CH_2), 56.48, 63.27 (CH_2), 114.35, 117.48, 119.80, 121.00, 126.68, 128.76, 129.54, 135.33 (ipso), 136.32 (ipso), 138.52 (ipso); HRMS (EI) *m/z* 242.1425 (calcd for $C_{15}H_{18}N_2O$ (M^+) 242.1419). Anal. Calcd for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found C, 74.50; H, 7.45; N, 11.30.

(1*S*)-(2-Nitrophenoxy)-1-*N*-(4-toluenesulfonyl)-1-phenylaminoethane (117)



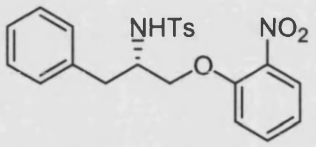
(*S*)-2-(*N*-Tosylamino)-2-phenylethanol (500mg, 2.2mmol) and 2-fluoronitrobenzene (232µl, 2.2mmol) were taken up in dry THF (15ml). To this mixture was added NaO*t*Bu (529mg, 5.5mmol). The reaction was stirred at room temperature for 20 hours. The solvent was evaporated and the mixture was taken up in DCM. The suspension was then filtered through Celite. The crude product was purified by flash column chromatography (eluent: ethyl acetate - *n*-hexane, 3:7 v/v) to give after evaporation of solvent a colourless solid (736mg, 81%). This was recrystallised from DCM - cyclohexane (1:1 v/v) to give colourless needles. Tlc (*n*-hexane - ethyl acetate, 1:1 v/v) R_f 0.42; m.p. 119-120 °C; $[\alpha]_D^{20}$ -142.6 (c 0.51, $CHCl_3$); δ_H ($CDCl_3$) 2.33 (s, 3**H**), 4.23 (dd, 1**H**, *J* 4.5, 9.2), 4.29 (dd, 1**H**, *J* 4.4, 9.1), 4.72 (ddd, 1**H**, *J* 4.4, 4.7, 6.7), 5.77 (d, 1**H**, *J* 6.7, N<u>H</u>), 6.90 (dd, 1**H**, *J* 1.0, 8.3), 7.05 (ddd, 1**H**, *J* 1.2, 7.2, 8.3), 7.11 (d, 2**H**, *J* 7.9), 7.24 (m, 5**H**), 7.48 (ddd, 1**H**, *J* 1.8, 7.2, 8.3), 7.59 (d, 2**H**, *J* 8.5), 7.89 (dd, 1**H**, *J* 1.8, 8.2); δ_C ($CDCl_3$) 21.89 (CH_3), 57.24, 72.84 (CH_2), 114.81, 121.46, 126.33, 127.30, 127.45, 128.31, 128.74, 129.61, 134.79, 137.10 (ipso), 139.49 (ipso), 143.45 (ipso), 151.76 (ipso); HRMS (FAB) *m/z* 413.1163 (calcd for $C_{21}H_{21}N_2O_5S$ (MH^+) 413.1172); Anal. Calcd for $C_{21}H_{20}N_2O_5S$: C, 61.15; H, 4.89; N, 6.79. Found: C, 61.00; H, 4.89; N, 6.84.

(1*S*)-2-(2-aminophenoxy)-1-*N*-(4-toluenesulfonyl)-1-phenylaminoethane (68)



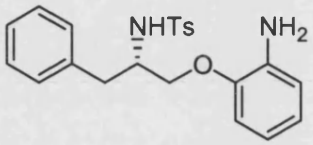
(1*S*)-(2-Nitrophenoxy)-1-*N*-(4-toluenesulfonyl)-1-phenylaminoethane **(116)** (391mg, 0.95mmol) was taken up in abs. EtOH (100ml). To the solution was added 10%Pd on carbon and the reaction with hydrogen was carried out as for **66** above to give a colourless crystalline powder (340mg, 94%). This was recrystallised from DCM-cyclohexane (1:1, v/v) to give colourless needles. Tlc (methanol-DCM, 1:9 v/v) R_f 0.79; m.p. 138-139 °C; $[\alpha]_D^{20}$ -52.6 (c 0.57, $CHCl_3$); IR (nujol mull) ν_{max} 3347, 3365, 3302; δ_H ($CDCl_3$) 2.34 (s, 3**H**), 3.63 (br. s, 2**H**, N$\underline{H}_2$), 4.05 (d, 2**H**, *J* 5.6), 4.71 (dd, 1**H**, *J* 5.9, 12.0), 5.85 (d, 1**H**, *J* 6.4, N$\underline{H}$), 6.59 (m, 1**H**), 6.61 (dd, 1**H**, *J* 1.5, 7.0), 6.65 (dd, 1**H**, *J* 1.5, 7.6), 6.77 (dt, 1**H**, *J* 1.8, 6.8, 7.9), 7.11 (d, 2**H**, *J* 7.9), 7.22 (m, 5**H**), 7.61 (d, 2**H**, *J* 8.2); δ_C ($CDCl_3$) 21.90 (CH_3), 57.47, 71.35 (CH_2), 112.29, 115.65, 118.54, 122.20, 127.14, 127.23, 128.16, 128.75, 129.63, 136.56 (ipso), 137.35 (ipso), 143.42 (ipso), 145.72 (ipso); HRMS (EI) *m/z* 382.1347 (calcd for M^+ 382.1351); Anal. Calcd for $C_{21}H_{22}N_2O_3S$: C, 65.9; H, 5.80; N, 7.32. Found: C, 65.9; H, 5.82; N, 7.28.

(2*S*)-1-(2-Nitrophenoxy)-2-*N*-(4-toluenesulfonyl)-3-phenyl-2-aminopropane (118)



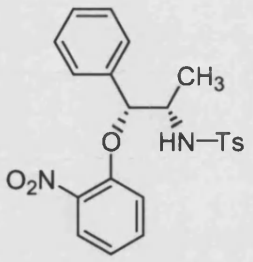
(*S*)-*N*-Tosylphenylalaninol (1.24g, 4.06mmol) and 2-fluoronitrobenzene (428.4ml, 4.06mmol) were taken up in dry THF (20ml). To the mixture was added NaO*t*Bu (976mg, 10.2mmol). The reaction was carried out as for **117** above to give, after purification, a yellow crystalline powder (1.64g, 92%). Tlc (*n*-hexane - ethyl acetate, 1:1 v/v) R_f 0.56; m.p. 100-101 °C; $[\alpha]_D^{23}$ +4.81 (c 1.04, $CHCl_3$); IR ($CDCl_3$) ν_{max} 3299; δ_H ($CDCl_3$) 2.34 (s, 3**H**), 2.83 (dd, 1**H**, *J* 6.9, 13.6), 3.00 (dd, 1**H**, *J* 7.9, 13.5), 3.79 (m, 1**H**), 3.92 (dd, 1**H**, *J* 4.7, 9.4), 4.01 (dd, 1**H**, *J* 2.9, 9.1), 5.35 (d, 1**H**, *J* 8.2, NH), 6.83 (dd, 1**H**, *J* 0.9, 8.5), 7.03 (m, 3**H**), 7.13 (d, 2**H**, *J* 8.5), 7.16 (m, 3**H**), 7.45 (ddd, 1**H**, *J* 1.8, 7.5, 8.5), 7.61 (dd, 2**H**, *J* 1.8, 8.5), 7.86 (dd, 1**H**, *J* 1.8, 8.2); δ_C ($CDCl_3$) 21.93 (CH_3), 38.19 (CH_2), 54.63, 69.72 (CH_2), 114.73, 121.08, 126.10, 126.96, 127.02, 128.88, 129.45, 129.86, 134.75, 136.82 (ipso), 137.49 (ipso), 139.53 (ipso), 143.51 (ipso), 151.91 (ipso); HRMS (FAB) *m/z* 427.1321 (calcd for $C_{22}H_{23}N_2O_5S$ (MH^+) 427.1328).

(2*S*)-1-(2-aminophenoxy)-2-*N*-(4-toluenesulfonyl)-3-phenyl-2-aminopropane (69)



(2*S*)-1-(2-Nitrophenoxy)-2-*N*-(4-toluenesulfonyl)-3-phenyl-2-aminopropane (**117**) (1.11g, 2.39mmol) and 10% Pd on carbon (96mg) were taken up in abs. ethanol (150ml). The reaction with hydrogen was carried out as for **68** above to give a pale brown solid (**69**, 835mg, 88%). Tlc (methanol - DCM, 1:9 v/v) R_f 0.69; m.p. 130-132 °C; $[\alpha]_D^{23}$ -20.8 (c 1.0, $CHCl_3$); IR (nujol mull) ν_{max} 3484, 3386, 3316; δ_H ($CDCl_3$) 2.38 (s, 3**H**), 2.88 (dd, 1**H**, *J* 5.7, 13.6), 2.95 (dd, 1**H**, *J* 7.0, 13.8), 3.81 (m, 5**H**), 5.27 (d, 1**H**, *J* 7.3, NH), 6.55 (d, 1**H**, *J* 8.2), 6.63 (ddd, 1**H**, *J* 1.5, 7.6, 7.6), 6.69 (d, 1**H**, *J* 7.6), 6.79 (ddd, 1**H**, *J* 1.2, 7.3, 7.6), 7.04 (m, 2**H**), 7.16 (d, 2**H**, *J* 7.9), 7.20 (m, 3**H**), 7.64 (d, 2**H**, *J* 7.9); δ_C ($CDCl_3$) 21.94 (CH_3), 38.86 (CH_2), 54.65, 68.77 (CH_2), 112.01, 115.60, 118.65, 122.01, 126.99, 127.07, 128.89, 129.53, 129.89, 136.44 (ipso), 136.75 (ipso), 137.59 (ipso), 143.51 (ipso), 145.96 (ipso); HRMS (EI) *m/z* 396.1508 (calcd for $C_{22}H_{24}N_2O_3S$ (M^+) 396.1507).

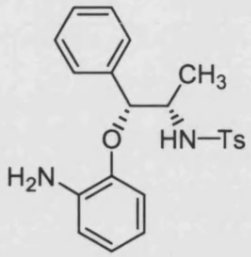
(1*R*,2*S*)-1-(2-Nitrophenoxy)-1-phenyl-2-*N*-(4-toluenesulfonyl)-2-aminopropane (119)



(1*R*,2*S*)-*N*-Tosyl-norephedrine (947mg, 3.1mmol) and 2-fluoronitrobenzene (327µl, 3.1mmol) were taken up in dry THF (50ml) and to the solution was added NaO*t*-Bu (745mg, 7.75mmol). The reaction was carried out as for **117** above to give a yellow powder. This was recrystallised from DCM - cyclohexane (1:1, v/v) to give pale yellow needles (496mg, 38%). Tlc (*n*-hexane - ethyl acetate, 6:4 v/v) R_f 0.46; m.p. 148 °C; $[\alpha]_D^{20}$ +200.9 (c 1.07, $CHCl_3$); IR (nujol mull) ν_{max} 3272; δ_H ($CDCl_3$) 0.98 (d, 3**H**, *J* 6.7), 2.34 (s, 3**H**), 3.79 (ddq, 1**H**, *J* 2.6, 6.7, 9.7), 5.33 (d, 1**H**, *J* 2.6), 5.42 (d, 1**H**, *J* 9.7, N<u>H</u>), 6.52 (d, 1**H**, *J* 8.5), 6.98 (ddd, 1**H**, *J* 1.2, 7.9, 8.2), 7.17 (d, 2**H**, *J* 8.5), 7.24 (m, 3**H**), 7.31 (m, 4**H**), 7.74 (d, 2**H**, *J* 8.2), 7.86 (dd, 1**H**, *J* 1.5, 8.2);

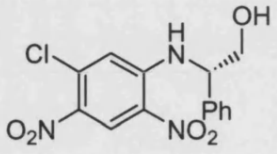
δ_C ($CDCl_3$) 14.21 (CH_3), 21.91 (CH_3), 55.38, 84.30, 116.19, 121.03, 125.80, 125.97, 126.87, 128.57, 129.13, 129.85, 134.35, 136.55 (ipso), 138.55 (ipso), 139.73 (ipso), 143.43 (ipso), 151.45 (ipso); HRMS (FAB) *m/z* 427.1322 (calcd for $C_{22}H_{23}N_2O_5S$ (MH^+) 427.1328); Anal. Calcd for $C_{22}H_{22}N_2O_5S$: C, 61.96; H, 5.20; N, 7.57. Found: C, 61.70; H, 5.17; N, 6.51.

(1*R*,2*S*)-1-(2-Aminophenoxy)-1-phenyl-2-*N*-(4-toluenesulfonyl)-2-aminopropane (70)



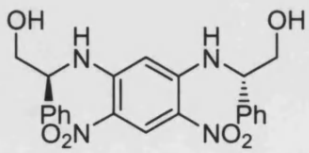
(1*R*,2*S*)-1-(2-Nitrophenoxy)-1-phenyl-2-*N*-(4-toluenesulfonyl)-2-aminopropane (**118**) (231mg, 0.54mmol) and 10%Pd on carbon (25mg) were taken up in abs. ethanol (100ml). The reaction was carried out as for **68** above to give a pale brown powder (179mg, 84%). Tlc (methanol-DCM, 1:9 v/v); R_f 0.69; m.p. 174-175 °C; $[\alpha]_D^{23}$ +60.4 (c 1.01, $CHCl_3$); δ_H ($CDCl_3$) 0.96 (d, 3**H**, *J* 7.0), 2.23 (s, 3**H**), 3.73 (ddq, 1**H**, *J* 2.9, 7.0, 9.7), 3.84 (br. s, 2**H**, N<u>H</u>$_2$), 4.88 (d, 1**H**, *J* 2.9), 5.47 (d, 1**H**, *J* 9.7, N<u>H</u>), 6.15 (dd, 1**H**, *J* 1.2, 8.2), 6.37 (ddd, 1**H**, *J* 2.0, 6.7, 8.2), 6.63 (dd, 1**H**, *J* 2.0, 7.9), 6.66 (m, 1**H**), 7.09 (d, 2**H**, *J* 8.5), 7.13 (d, 1**H**, *J* 7.0), 7.13 (d, 1**H**, *J* 8.2), 7.18 (m, 1**H**), 7.23 (m, 2**H**), 7.61 (dd, 2**H**, *J* 1.8, 8.2); δ_C ($CDCl_3$) 15.67 (CH_3), 21.94 (CH_3), 54.89, 82.50, 114.032, 115.86, 118.80, 122.01, 126.30, 126.94, 128.16, 128.83, 129.90, 136.52 (ipso), 137.65 (ipso), 138.39 (ipso), 143.39 (ipso), 145.76 (ipso); HRMS (EI) *m/z* 396.1502 (calcd for $C_{22}H_{24}N_2O_3S$ (M^+) 396.1508); Anal. Calcd for $C_{22}H_{24}N_2O_3S$: C, 66.64; H, 6.10; N, 7.07. Found: C, 66.70; H, 6.18; N, 7.02.

(*R*)-2-Phenyl-2-*N*-(5-chloro-2,4-dinitrophenyl)-2-aminoethanol (72)



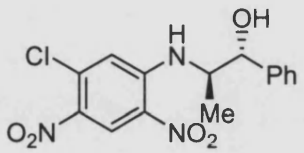
1,5-Dichloro-2,4-dinitrobenzene (**71**) (200mg, 0.84mmol) was taken up in MeCN (11ml). To this was added (*R*)-phenylglycinol (115mg, 0.84mmol) and Et_3N (164ml, 1.18mmol). The reaction was stirred at room temperature for four days, the solvent was evaporated and the product purified by flash column chromatography (ethyl acetate-light petroleum, 3:7 v/v) to give an orange oil (**72**, 257mg, 91%). Tlc (ethyl acetate-light petroleum, 3:7 v/v) R_f 0.29; $[\alpha]_D^{23}$ +186.9 (c 1.02, $CHCl_3$); IR (neat) ν_{max} 3546, 3352; δ_H ($CDCl_3$) 2.68 (br. s, 1**H**, O<u>H</u>), 3.93 (dd, 1**H**, *J* 6.5, 11.4), 4.08 (dd, 1**H**, *J* 4.0, 11.4), 4.76 (dd, 1**H**, *J* 6.1, 10.1), 6.76 (s, 1**H**), 7.37 (m, 5**H**), 8.98 (s, 1**H**), 9.18 (br. d, 1**H**, *J* 6.0, N<u>H</u>); δ_C ($CDCl_3$) 59.60, 66.35, 117.46, 126.46, 126.68, 128.77, 129.46, 134.84 (ipso), 135.57 (ipso), 136.85 (ipso), 146.30 (ipso); HRMS (FAB) *m/z* 338.0542 (calcd for $C_{14}H_{12}ClN_3O_5$ (MH^+) 338.0544).

2,4-*N*-Bis[(*R*)-2-hydroxy-1-phenylethyl]-1,5-dinitro-2,4-diaminobenzene (73)



(*R*)-Phenylglycinol (127mg, 0.93mmol) was taken up in dry MeCN (8ml) and to the solution was added 1,5-Dichloro-2,4-dinitrobenzene (**71**) (100mg, 0.42mmol) followed by triethylamine (165µl, 1.18mmol). The reaction was carried out as for **72** above and yielded a yellow solid (**73**, 166mg, 90%). Tlc (methanol - dichloromethane, 1:9 v/v) R_f 0.45; m.p. 99-100°C; $[\alpha]_D^{30}$ -44 (c 1, DCM); IR (nujol mull) ν_{max} 3343, 1622, 1573, 1546, 1411; δ_H ($CDCl_3$) 1.75 (s, 2**H**, O<u>H</u>), 3.74 (dd, 2**H**, *J* 6.2, 10.9), 3.86 (br. d, 2**H**, *J* 10.9), 3.96 (dd, 2**H**, *J* 5.1, 10.2), 5.19 (s, 1**H**), 7.20 (dd, 4**H**, *J* 1.6, 8.6), 7.39 (m, 2**H**), 7.45 (dd, 4**H**, *J* 7.8, 8.6), 8.93 (d, 2**H**, *J* 5.1, N<u>H</u>), 9.23 (s, 1**H**); δ_C ($CDCl_3$) 59.80, 66.76 (CH_2), 124.90 (ipso), 126.87, 128.70, 129.22 (ipso), 129.33, 137.31 (ipso), 147.62; HRMS (FAB) *m/z* 439.1618 (calcd for $C_{22}H_{23}N_4O_6$ (MH^+) 439.1618); Anal. Calcd for $C_{22}H_{22}N_4O_6$: C, 60.25; H, 5.06; N, 12.78. Found C, 59.50; H, 5.08; N, 12.10.

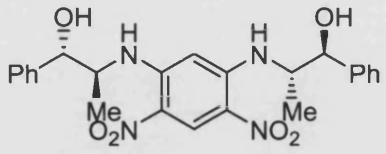
(1*R*,2*S*)-1-Phenyl-2-*N*-(5-chloro-2,4-dinitrophenyl)-2-amino propan-1-ol (74)



1,5-Dichloro-2,4-dinitrobenzene (**71**) (150mg, 0.63mmol) was taken up in dry MeCN (8ml). (1*R*,2*S*)-norephedrine (96mg, 0.63mmol) was added, followed by triethylamine (55.8µl) and the reaction was stirred at room temperature under

argon for three days. After this time the reaction was still incomplete by tlc and so the reaction was heated at 90°C for a further day. Evaporation of the solvent and purification by flash column chromatography yielded a yellow powder (**74**, 164mg, 74%). Tlc (ethyl acetate - light petroleum, 3:7 v/v) R_f 0.30; m.p. 163-165 °C; $[\alpha]_D^{24}$ +92 (c 1.0, $CHCl_3$); IR (KBr) ν_{max} 3594, 3340; δ_H ($CDCl_3$) 1.25 (d, 3**H**, *J* 6.6), 2.33 (br. s, 1**H**, NH), 4.05 (m, 1**H**), 4.97 (d, 1**H**, *J* 3.9), 7.00 (s, 1**H**), 7.38 (m, 5**H**), 8.69 (d, 1**H**, *J* 8.6, NH), 9.04 (s, 1**H**); δ_C ($CDCl_3$) 15.40(CH_3), 54.58, 76.40, 116.85, 126.41, 127.25, 128.86, 129.00, 129.17 (ipso), 134.50 (ipso), 135.84 (ipso), 139.69 (ipso), 146.34 (ipso); HRMS (FAB) *m/z* 352.0707 (calcd for $C_{15}H_{15}ClN_3O_5$ (MH^+) 352.0701); Anal. Calcd for $C_{15}H_{14}ClN_3O_5$: C, 51.20; H, 4.00; N, 11.90. Found C, 51.40; H, 4.17; N, 11.70.

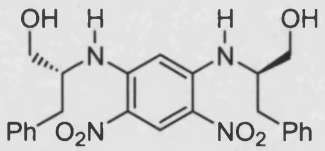
2,4-*N*-Bis-[(1R,2S)-1-hydroxy-1-phenyl-prop-2-yl]-1,5-dinitro-2,4-diaminobenzene (75)



1,5-Dichloro-2,4-dinitrobenzene (**71**) (301.8mg, 1.27mmol) and (1*R*,2*S*)-norephedrine (404.8mg, 2.67mmol) were taken up in dry MeCN (8ml) and to the solution was added triethylamine (760µl, 5.5mmol). The reaction was stirred at room temperature for 30 hours after which tlc analysis showed the

reaction to be incomplete. The reaction was heated at reflux for 2 days. The product was purified by flash column chromatography (gradient elution; 100% DCM to methanol - DCM, 5:95 v/v) to give the product after drying *in vacuo,* as a yellow powder (**75**, 570mg, 96%). Tlc (methanol - dichoromethane, 3:7 v/v) R_f 0.63; m.p. 99-98 °C. $[\alpha]_D^{30}$ +11.8 (c 1.0, CH_2Cl_2); IR (nujol mull) ν_{max} 3460, 3341, 1619, 1571, 1455, 1409; δ_H ($CDCl_3$) 1.24 (d, 6**H**, *J* 6.6), 2.03 (s, 2**H**, O<u>H</u>), 3.91 (m, 2**H**), 4.96 (d, 2**H**, *J* 4.0), 5.92 (s, 1**H**), 7.34 (m, 10**H**), 8.53 (d, 2**H**, N<u>H</u>), 9.18 (s, 1**H**); δ_C ($CDCl_3$) 14.77 (CH_3), 53.98, 75.79, 91.32, 124.11 (ipso), 126.16, 128.30, 128.65, 129.78, 140.20 (ipso), 147.79 (ipso); HRMS (FAB) *m/z* 467.1934 (calcd for $C_{24}H_{27}N_4O_6$ (MH^+) 467.1931); Anal. calcd for $C_{24}H_{26}N_4O_6$: C, 61.79; H, 5.62; N, 12.01. Found C, 61.40; H, 5.78; N, 11.70.

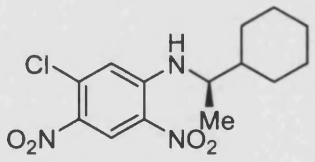
2,4-*N*-Bis[(*R*)-2-hydroxy-1-benzylethyl]-1,5-dinitro-2,4-diaminobenzene (76)



1,5-Dichloro-2,4-dinitrobenzene (**71**) (260mg, 1.1mmol) and (*S*)-phenylalaninol (365mg, 2.41mmol) were taken up in dry MeCN (12ml). To the solution was added triethylamine (670µl, 4.8mmol). The reaction, carried out in similar fashion to **75,** afforded a yellow powder (318mg, 62%). Tlc (*n*-

hexane - ethyl acetate, 1:1 v/v) R_f 0.16; m.p. 133-134 °C; $[\alpha]_D^{30}$ -88 (c 1.0, DCM); IR (KBr) ν_{max} 3463, 3351; δ_H ($CDCl_3$) 1.98 (br. s, 2**H**, O<u>H</u>), 2.94 (dd, 2**H**, *J* 6.4, 13.7), 3.03 (dd, 2**H**, *J* 5.9, 13.7), 3.75 (m, 3**H**), 5.71 (s, 1**H**), 7.26 (m, 10**H**), 8.57 (d, 2**H**, *J* 7.3, N<u>H</u>), 9.15 (s, 1**H**); δ_C ($CDCl_3$) 37.52, 56.04, 63.41, 91.36, 124.18 (ipso), 126.98, 128.83, 129.25, 129.71, 137.08 (ipso), 148.14 (ipso); HRMS (FAB) *m/z* 467.1932 (calcd for $C_{24}H_{27}N_4O_6$ (MH^+) 467.1931); Anal. Calcd for $C_{24}H_{26}N_4O_6$: C, 61.79; H, 5.62; N, 12.01. Found C, 62.00; H, 5.76; N, 11.90.

(*R*)-1-*N*-(5-chloro-2,4dinitrophenyl)-1-cyclohexyl-1-aminoethane (77)



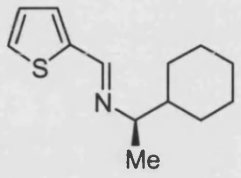
1,5-Dichloro-2,4-dinitrobenzene (**71**) (300mg, 1.26mmol) was taken up in dry MeCN (8ml) and to the solution was added (*R*)(-)-cyclohexylethylamine (188.2µl, 1.26 mmol) and triethylamine (210.8µl, 1.51 mmol). The reaction was carried out as for **72** above to obtain a yellow solid (397mg, 96%). The product was recrystallised from ethyl acetate-*n*-hexane (5:95 v/v) to give a yellow powder. Tlc (ethyl acetate - *n*-hexane, 2:8 v/v) R_f 0.55; m.p. 105-106 °C; $[\alpha]_D^{22}$ -126.8 (c 1.1, $CHCl_3$); IR (KBr): ν_{max} 3347.5;

δ_H ($CDCl_3$) 1.19 (m, 5**H**), 1.27 (d, 3**H**, *J* 6.6), 1.57 (m, 1**H**), 1.79 (m, 5**H**), 3.59 (dq, 1**H**, *J* 6.6, 14.4), 6.95 (s, 1**H**), 8.52 (d, 1**H**, *J* 7.8), 9.07 (s, 1**H**);

δ_C ($CDCl_3$) 17.47 (CH_3), 26.09 (CH_2), 26.16 (CH_2), 26.25 (CH_2), 28.97 (CH_2), 29.23 (CH_2), 43.08, 54.13, 116.03, 127.16, 128.60 (ipso), 133.87 (ipso), 135.71 (ipso), 146.25 (ipso); HRMS (EI) *m/z* 327.0982 (calcd for $C_{14}H_{18}ClN_3O_4$ (M^+) 327.0986); Anal. Calcd for $C_{14}H_{18}ClN_3O_4$: C, 51.3; H, 5.54; N, 12.82. Found C, 51.20; H, 5.55; N, 12.70.

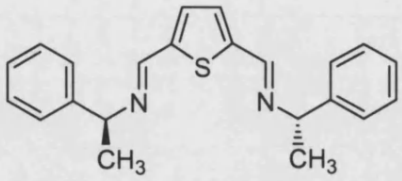
6.5 EXPERIMENTAL FOR CHAPTER 4

Thiophene-2-carboxaldehyde-(*R*)-1-cyclohexylethyl imine (86)



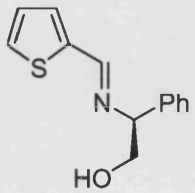
(*R*)-(-)-1-Cyclohexylethylamine (318µl, 2.14mmol) was taken up in anhydrous methanol (4ml) and the solution was stirred, under argon, at 80°C. To this hot solution was added 2-thiophenecarboxaldehyde (200µl, 2.14mmol) in anhydrous methanol (1ml) over a period of 35 minutes. The reaction was stirred for 5 hours after which IR analysis showed that the reaction was complete. The solvent was evaporated *in vacuo*, to leave a colourless oil (**86**, 470mg, 100%). IR (neat) ν_{max} 1634; δ_H ($CDCl_3$) 0.89 (m, 2**H**), 1.18 (m, 3**H**), 1.21 (d, 3**H**, *J* 6.4), 1.47 (m, 1**H**), 1.73 (m, 5**H**), 2.96 (dq, 1**H**, *J* 6.4, 13.2), 7.05 (dd, 1**H**, *J* 3.9, 4.9), 7.27 (dd, 1**H**, *J* 1.0, 3.4), 7.36 (d, 1**H**, *J* 4.9), 8.29 (s, 1**H**); δ_C ($CDCl_3$) 19.84 (CH_3), 26.21 (CH_2), 26.39 (CH_2), 26.57 (CH_2), 29.81 (CH_2), 30.08, 43.62, 71.82, 127.23, 128.25, 129.74, 142.85 (ipso), 151.81; HRMS (FAB) *m/z* 222.1316 [calcd for $C_{13}H_{20}NS$ (MH^+) 221.1317].

(*S*)-1-[(2,5-dimethylimino)thiophene]-1-phenylethane (87)



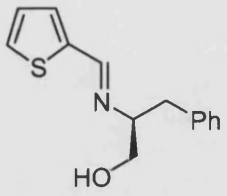
(*S*)-α-Methylbenzylamine (276µl, 2.14mmol) and taken up in dry methanol (5ml). The solution was heated to 80°C and 2,5-thiophene-2,5-biscarboxaldehyde (150mg, 1.07mmol) was added in methanol solution (2ml) over a period of 30 minutes. The reaction was allowed to reflux for 15 hours until complete. The solvent was evaporated to leave a colourless solid (372mg, 100%) A portion was recrystallised from DCM - cyclohexane (1:1 v/v) to give colourless crystals. M.p. 166-167 °C; IR (nujol mull) ν_{max} 1621, 1459, 1376; $[\alpha]_D^{19}$ +673 (c 1.0, DCM); δ_H ($CDCl_3$) 1.56 (d, 6**H**, *J* 6.7), 4.52 (q, 2**H**, *J* 6.6), 7.22 (s, 2**H**), 7.24 (m, 2**H**), 7.33 (m, 4**H**), 7.40 (m, 4**H**), 8.37 (s, 2**H**); δ_C ($CDCl_3$) 25.48 (CH_3), 69.69, 126.80, 127.06, 128.61, 130.03, 145.16 (ipso), 145.35 (ipso), 152.55, 152.59; HRMS (FAB) *m/z* 347.1590 [calcd for $C_{22}H_{23}N_2S$ (MH^+) 347.1583]; Anal. calcd for $C_{22}H_{22}N_2S$: C, 76.30; H, 6.40; N, 8.08; Found C, 75.90; H, 6.42; N, 8.16.

Thiophene-2-carboxaldehyde-(*S*)-(2-hydroxy-1-phenylethyl)imine (88)



(*R*)-Phenylglycinol (440mg, 3.21mmol) was taken up in dry methanol (5ml). To the refluxing solution was added 2-thiophenecarboxaldehyde (300µl, 3.21mmol) and the reaction carried out as for **86** above to give near colourless crystals (623mg, 84%). The product was recrystallised from DCM - cyclohexane (1:1 v/v) to give colourless plates (426mg, 57%). M.p. 101-102 °C; $[\alpha]_D^{23}$ +154.5 (c 0.99, $CHCl_3$); IR (neat) ν_{max} 3364 (br), 1632; δ_H ($CDCl_3$) 2.49 (br. s. 1**H**, O<u>H</u>), 3.87 (dd, 1**H**, *J* 4.4, 11.2), 3.95 (dd, 1**H**, *J* 11.3, 8.2), 4.46 (dd, 1**H**, *J* 4.4, 8.3), 7.04 (dd, 1**H**, *J* 3.7, 5.1), 7.25 (dd, 1**H**, *J* 2.4, 6.4), 7.28 (dd, 1**H**, *J* 1.0, 3.4), 7.34 (dd, 2**H** *J* 6.8, 8.3), 7.40 (m, 3**H**), 8.43 (s, 1**H**); δ_C ($CDCl_3$) 67.66 (CH_2), 75.68, 127.37, 127.48, 128.55, 129.34, 131.17, 140.44(ipso), 142.105(ipso), 155.89; HRMS (FAB) *m/z* 232.0793 [calcd for $C_{13}H_{14}NOS$ (MH^+) 232.0797]; Anal. Calcd for $C_{13}H_{13}NOS$: C, 67.50; H, 5.66; N, 6.06. Found C, 67.20; H, 5.65; N, 6.09.

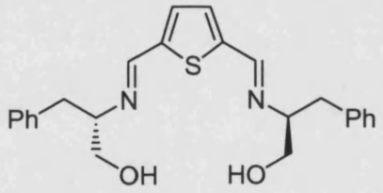
Thiophene-2-carboxaldehyde-(*S*)-(1-hydroxy-3-phenylprop-2-yl)imine (89)



(*S*)-Phenylalaninol (486mg, 3.21mmol) was taken up in anhydrous methanol (5ml) and to the refluxing solution was added 2-thiophene carboxaldehyde (300µl,3.21 mmol) in methanol as for **86** above. The reaction yielded a colourless solid (798mg, 100%) which was recystallised from DCM -

cyclohexane (1:1 v/v) to give colourless needles (198mg, 25%). $[\alpha]_D^{24}$ -335.4 (c 1.1, $CHCl_3$); IR (KBr) ν_{max} 1630; δ_H ($CDCl_3$) 2.19 (br. s. 1**H**, OH), 2.82 (dd, 1**H**, *J* 8.5, 13.4), 2.92 (dd, 1**H**, *J* 5.1, 13.4), 3.46 (dt, 1**H**, *J* 5.8, 7.7), 3.76 (dd, 1**H**, *J* 3.7, 11.0), 3.82 (dd, 1**H**, *J* 7.3, 11.2), 6.98 (dd, 1**H**, *J* 3.7, 5.1), 7.13 (m, 4**H**), 7.22 (m, 2**H**), 7.34 (d, 1**H**, *J* 4.9), 7.99 (s, 1**H**); δ_C ($CDCl_3$) 38.65 (CH_2), 65.64 (CH_2), 74.00, 126.09, 127.26, 128.17, 128.97, 129.62, 130.82, 138.45(ipso), 141.63(ipso), 155.47; HRMS (FAB) *m/z* 246.0954 [calcd for $C_{14}H_{16}NOS$ (MH^+) 246.0593].

Thiophene-2,5-dicarboxaldehyde-bis[(*S*)-1-hydroxy-3-phenylprop-2-yl]imine (90)

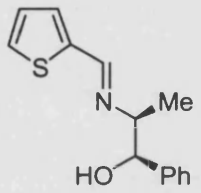


(*S*)-Phenylalaninol (216mg, 1.43mmol) was taken up in dry MeOH (5ml). The solution was brought to reflux and to it was added 2,5-thiophene dicarboxaldehyde (100mg, 0.71mmol). The reaction was carried out as for **86** above and yielded colourless crystals (291mg, 100%). M.p. 113-116 °C; $[\alpha]_D^{23}$ -780 (c 1.0, $CHCl_3$); IR (neat) ν_{max} 3364, 1628; δ_H ($CDCl_3$) 2.82 (dd, 2**H**, *J* 8.5, 13.4), 2.84 (br. s, 2**H**), 2.93 (dd, 2**H**, *J* 4.6, 13.4), 3.49 (dddd, 2**H**, *J* 3.9, 4.4, 7.3, 8.3), 3.79 (dd, 2**H**, *J* 3.9, 11.2), 3.85 (dd, 2**H**, *J* 7.3, 11.2),

6.90 (s, 2**H**), 7.10 (d, 2**H**, *J* 8.3), 7.12 (d, 2**H**, *J* 6.4) 7.14 (dd, 2**H**, *J* 6.4, 1.0) 7.18 (d, 4**H**, *J* 7.8), 7.88 (s, 2**H**);

δ_C ($CDCl_3$) 38.75 (CH_2), 65.75 (CH_2), 74.29, 126.15, 128.25, 129.66, 130.52, 138.44 (ipso), 144.07 (ipso), 155.39; HRMS (FAB) *m/z* 407.1787 [calcd for $C_{24}H_{27}N_2O_2S$ (MH^+) 407.1794].

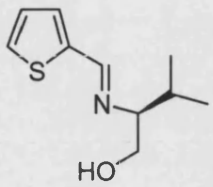
Thiophene-2-carboxaldehyde-[(1*R*,2*S*)-1-hydroxy-1-phenylprop2-yl]imine (91)



(1*R*,2*S*)-Norephedrine (324mg, 2.14mmol) was taken up in dry methanol (6ml). To the refluxing solution was slowly added 2-thiophene carboxaldehyde (200µl, 2.14mmol) and the reaction carried out as for **86** above to give a yellow oil (527mg, 100%). $[\alpha]_D^{30}$ +50.2 (c 1.95, CH_2Cl_2); IR (neat) ν_{max} 3366, 1631.

δ_H ($CDCl_3$) 1.13 (d, 3**H**, *J* 6.4), 3.25 (br. s., 1**H**), 3.55 (q, 1**H**, *J* 5.4), 4.78 (d, 1**H**, *J* 3.4), 6.90 (dd, 1**H**, *J* 3.6, 5.0), 7.12 (d, 1**H**, *J* 3.5), 7.16 (d, 1**H**, *J* 7.0), 7.23 (m, 3**H**), 7.33 (d, 1**H**, *J* 6.8), 8.24 (s, 1**H**); δ_C ($CDCl_3$) 15.99(CH_3), 70.42, 76.53, 126.51, 127.11, 127.23, 127.89, 128.91, 130.47, 141.17 (ipso), 142.29(ipso), 153.55; HRMS (FAB) *m/z* 246.0964 [calcd for $C_{14}H_{16}NOS$ (MH^+) 246.0953].

Thiophene-2-carboxaldehyde[(*S*)-1-hydroxy-3methylbut-2-yl]imine (92)

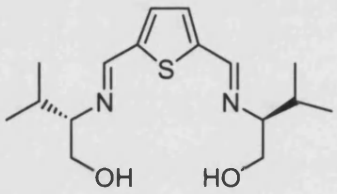


(*S*)-Valinol (802mg, 7.78mmol) was taken up in anhydrous methanol (10ml) and activated 3Å sieves were added. The solution was brought to reflux and 2-thiophenecarboxaldehyde (726µl, 7.77mmol) was added; the reaction was carried out as for **86** above. The crude product was recrystallised from diethyl ether to give colourless needles (821mg, 54%). M.p. 79-80 °C; $[\alpha]_D^{27}$ -98.06 (c 1.0, $CHCl_3$); IR (nujol mull) ν_{max} 3274, 1631.

δ_H ($CDCl_3$) (major isomer) 0.86 (d, 3**H**, *J* 6.6), 0.95 (d, 3**H**, *J* 6.6), 1.92 (dqq, 1**H**, *J* 6.6, 6.6, 7.0), 2.06 (br.s, 1**H**), 2.92 (ddd, *J* 3.9, 7.0, 7.4), 3.79 (m, 2**H**), 7.06 (ddd, 1**H**, *J* 1.2, 3.5, 5.1), 7.29 (dd, 1**H**, *J* 1.2, 3.5), 7.39 (dt, 1**H**, *J* 1.2, 5.1), 8.34 (s, 1**H**); δ_H ($CDCl_3$) (minor isomer) 0.91 (2 x d, *J* 6.6), 1.07 (2 x d, *J* 6.6), 1.65 (dqq), 3.12 (m), 3.47 (m), 4.02 (m), 5.69 (s), 5.79 (s), 6.98 (m), 7.14 (dd, *J* 1.2, 3.5), 7.25 (dd, *J* 1.2, 5.1); δ_H (CD_3CN) 0.86 (d, 3**H**, *J* 6.8), 0.90 (d, 3**H**, *J* 6.8), 1.85 (sex, 1**H**, *J* 6.6), 2.55 (br. m, 1**H**, OH), 2.91 (ddd, 1**H**, *J* 3.7, 6.1, 8.2), 3.53 (ddd, 1**H**, *J* 5.7, 8.2, 11.0), 3.70 (ddd, 1**H**, *J* 3.7, 6.6, 11.0), 7.11 (dd, 1**H**, *J* 3.6, 5.0), 7.37 (dd, 1**H**, *J* 1.0, 3.5), 7.47 (d, 1**H**, *J* 5.1), 8.35 (s, 1**H**); δ_C ($CDCl_3$) 19.93 (CH_3), 20.04 (CH_3), 30.36, 64.51 (CH_2), 64.81, 79.07, 127.50, 129.04, 130.76, 142.30 (ipso), 155.11; HRMS (EI) *m/z* 197.0859 [calcd for $C_{10}H_{15}NOS$ (M^+)

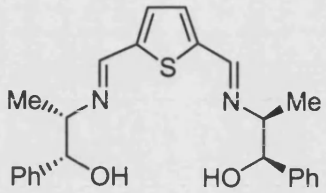
197.0874]; Anal. calcd for $C_{10}H_{15}NOS$: C, 60.88; H, 7.66; N, 7.10. Found C, 60.80; H, 7.68; N, 7.07.

Thiophene-2,5-dicarboxaldehyde-bis[(*S*)-1-hydroxy-3-methylbut-2-yl]imine (93)



(*S*)-Valinol (467mg, 4.53mmol) was taken up in dry methanol (10ml). 3Å molecular sieves were added together with 2,5-thiophenecarboxaldehyde (317mg, 2.26mmol). The reaction was carried out as for **86** above to give a yellow solid. This was recrystallised from diethyl ether to give a yellow crystalline powder (545mg, 78%). M.p. 97-98 °C; $[\alpha]_D^{27}$ -103.4 (c 1.03, $CHCl_3$); IR (nujol mull) ν_{max} 3284, 1630; δ_H (CD_3CN) 0.86 (d, 6**H**, *J* 6.8), 0.90 (d, 6**H**, *J* 6.8), 1.87 (dqq, 2**H**, *J* 6.6, 6.8, 6.8), 2.60 (br. s, 2**H**), 2.93 (m, 2**H**), 3.54 (m, 2**H**), 3.69 (dd, 2**H**, *J* 11.0, 3.3), 7.33 (s, 2**H**), 8.31 (s, 2**H**); δ_C ($CDCl_3$) 19.72 (CH_3), 20.08 (CH_3), 30.43, 64.81(CH_2), 78.94, 130.43, 144.82 (ipso), 154.90; HRMS (EI) *m/z* 310.1722 [calcd for $C_{16}H_{26}N_2O_2S$ (M^+) 310.1715]; Anal. calcd for $C_{16}H_{26}N_2O_2S$: C, 61.90; H, 8.44; N, 9.02. Found C, 61.90; H, 8.47; N 8.68.

Thiophene-2,5-dicarboxaldehyde-bis[(1*R*,2*S*)-1-hydroxy-1-phenylprop-2-yl]imine (94)

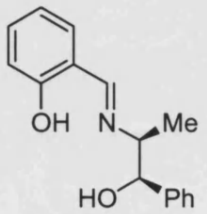


To a refluxing solution of (1*R*,2*S*)(-)-norephedrine (151mg, 1mmol) in anhydrous methanol was added 2,5-thiophenedicarboxaldehyde (70 mg, 0.5mmol) and the reaction was carried out as for **86** above. The reaction afforded a white solid which was recrystallised from cyclohexane - DCM (1:1 v/v) to give colourless needles (69mg, 29%). Mp 130-131 °C; $[\alpha]_D^{30}$ +128.7 (c 1.0, $CHCl_3$); IR (KBr) ν_{max} 3446, 1617.

δ_H ($CDCl_3$) 1.13 (d, 6**H**, *J* 6.6), 2.91 (br. s, 2**H**), 3.64 (m, 2**H**), 4.83 (d, 2**H**, *J* 4.4), 7.23 (s, 2**H**), 7.28 (m, 2**H**), 7.36 (m, 8**H**), 8.29 (s, 2**H**);

δ_C ($CDCl_3$) 16.12, 70.56, 76.87, 126.59, 127.36, 128.09, 130.31, 140.96, 144.97, 153.55; HRMS (FAB) *m/z* 407.1786 [calcd for $C_{24}H_{27}N_2O_2S$ (MH^+) 407.1794]; Anal. Calcd for $C_{24}H_{26}N_2O_2S$: C, 70.91; H, 6.45; N, 6.89. Found C, 70.70; H, 6.46; N, 6.91.

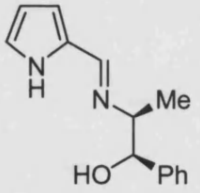
2-hydroxybenzaldehyde[(1*R*,2*S*)-1-hydroxy-1-phenylprop-2-yl]imine (95)



(1*R*,2*S*)-Norephedrine (285mg, 1.88mmol) was taken up in dry methanol (6ml) and to the solution was added salicylaldehyde (200µl, 1.88mmol). The reaction was carried out as for **86** above to yield a yellow oil (484mg, 100%). $[\alpha]_D^{15}$ +116.9 (c 0.59, $CHCl_3$); IR (DCM) ν_{max} 1632.

δ_H ($CDCl_3$) 1.20 (d, 3**H**, *J* 6.3), 3.54 (dq, 1**H**, *J* 5.9, 6.4), 4.63 (d, 1**H**, *J* 5.4), 6.77 (dd, 1**H**, *J* 7.8, 7.3), 6.86 (d, 1**H**, *J* 8.3), 6.92 (d, 1**H**, *J* 7.8), 7.20 (dd, 1**H**, *J* 1.0, 8.3), 7.25 (m, 5**H**), 8.08 (s, 1**H**); δ_C ($CDCl_3$) 17.78 (CH_3), 69.37, 77.20, 117.00, 118.35 (ipso), 118.62, 126.76, 127.57, 127.95, 131.33, 132.27, 140.81 (ipso), 161.47 (ipso), 164.38; HRMS (FAB) *m/z* 256.1332 (calcd for $C_{16}H_{18}NO_2$ (MH^+ 256.1338).

Pyrrole-2-carboxaldehyde [(1*R*,2*S*)-1-hydroxy-1-phenylprop-2-yl]imine (96)

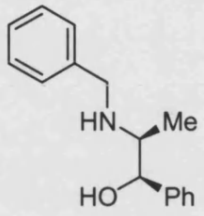


(1*R*,2*S*)-Norephedrine (332mg, 2.2mmol) was taken up in dry methanol (8ml) and to solution was added pyrrole-2-carboxaldehyde (209mg, 2.2mmol) following a similar procedure to **86** above. The reaction yielded an off-white crystalline powder (299mg, 60%). M.p. 80 °C; $[\alpha]_D^{30}$ +9.45 (c 2.0, CH_2Cl_2); IR (DCM) ν_{max} 3290, 1634. δ_H ($CDCl_3$) 1.11 (d, 3**H**, *J* 6.4), 3.52 (m, 1**H**), 4.87 (d, 1**H**, *J* 2.8), 6.16 (m, 1**H**), 6.48 (d, 1**H**, *J* 3.4), 6.59 (br. s, 1**H**),

7.27 (d, 1**H**, *J* 7.9), 7.36 (m, 2**H**), 7.41 (d, 2**H**, *J* 7.3), 8.06 (s, 1**H**); δ_C ($CDCl_3$) 15.44 (CH_3), 71.09, 77.31, 109.68, 115.46, 122.34, 126.36, 127.24, 128.19, 129.56 (ipso), 141.69 (ipso), 151.65; Anal. calcd for $C_{14}H_{16}N_2O$: C, 73.66; H, 7.06; N, 12.27. Found C, 73.50; H, 7.10; N, 12.30.

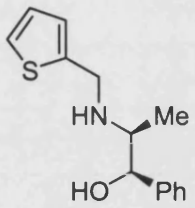
6.6 EXPERIMENTAL FOR CHAPTER 5

(1*R*, 2*S*)-*N*-Benzyl-2-amino-1-phenylpropan-1-ol (98)



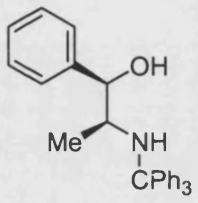
(1*R*,2*S*)-Norephedrine (939mg, 6.2mmol) and sodium cyanoborahydride (392mg, 6.2mmol) were taken up in anhydrous methanol (10ml). To this was slowly added benzaldehyde (692mg, 6.5mmol) in similar fashion to **99**. The crude product was taken up in EtOAc and the organic solution washed with saturated NH_4Cl solution and then with brine. The combined organic phases were dried over Na_2SO_4 and the crude product purified by flash chromatography (eluent: *n*-hexane - ethyl acetate, 8:2 v/v) affording a colourless oil (1.072g, 72%). Tlc (methanol - DCM, 1:9 v/v) R_f 0.38; $[\alpha]_D^{23}$ -24.0 (c 0.48, $CHCl_3$); IR (thin film) ν_{max} 3407 (br); δ_H ($CDCl_3$) 0.85 (d, 3**H**, *J* 6.4), 2.94 (dq, 1**H**, *J* 3.8, 6.5), 3.14 (br. s, 2**H**), 3.78 (d, 1**H**, *J* 13.2), 3.84 (d, 1**H**, *J* 13.2), 4.75 (d, 1**H**, *J* 3.8), 7.26 (m, 10**H**); δ_C ($CDCl_3$) 14.75 (CH_3), 51.45 (CH_2), 58.18, 73.56, 126.39, 127.38, 127.56, 128.38, 128.47, 128.85, 139.77 (ipso), 141.58 (ipso); HRMS (FAB) *m/z* 242.1544 [calcd for $C_{16}H_{20}NO$ (MH^+) 242.1545].

(1*R*,2*S*)-1-Phenyl-2-*N*-(2-thiophenylmethyl)amino propan-1-ol (99)



(1*R*,2*S*)-Norephedrine (610mg, 4.0mmol) and $NaCNBH_3$ (255mg, 4.1mmol) were taken up in dry methanol (15ml). To this solution was added a solution of 2-thiophenecarboxaldehyde (414µl, 4.4mmol) in methanol (2ml) over 1.5 hours. The mixture was stirred at room temperature for 2 days, the solvent evaporated and the residue taken up in ethyl acetate. This was washed with $NaHCO_3$ solution and the aqueous phase back extracted three times with ethyl acetate. The combined organic phases were dried over Na_2SO_4. The solids were filtered off and the solvent evaporated to leave a crude oil. Purification by flash column chromatography (gradient elution, DCM followed by methanol - DCM, 5:95 v/v) gave a pale yellow oil (348mg, 35%). Tlc (methanol - DCM, 1:9 v/v) R_f 0.41; $[\alpha]_D^{22}$ -19.8 (c 1.82, $CHCl_3$); IR (thin film) ν_{max} 3405 (br); δ_H ($CDCl_3$) 0.90 (d, 3**H**, *J* 6.4), 3.03 (dq, 1**H**, *J* 3.8, 6.5), 4.02 (dd, 1**H**, *J* 0.7, 14.2), 4.10 (dd, 1**H**, *J* 0.7, 14.2), 4.76 (d, 1**H**, *J* 3.8), 6.95 (m, 1**H**), 6.98 (dd, 1**H**, *J* 3.5, 5.0), 7.24 (dd, 1**H**, *J* 1.2, 5.0), 7.28 (m, 1**H**), 7.34 (m, 4**H**); δ_C ($CDCl_3$) 15.07 (CH_3), 46.03 (CH_2), 57.65, 73.86, 124.80, 125.21, 126.44, 126.99, 127.36, 128.35, 141.54 (ipso), 144.09 (ipso); HRMS (FAB) *m/e* 248.1117 [calcd for $C_{14}H_{18}NOS$ (MH^+) 248.1109].

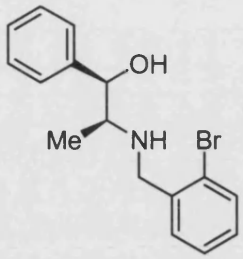
(1*R*,2*S*)-*N*-trityl-2-amino-1-phenylpropan-1-ol (100)



(1*R*,2*S*)-Norephedrine (910mg, 6mmol) was taken up in dry DCM (10ml) and to the solution was added Et_3N (980ml, 7mmol). The solution was cooled to 0°C and trityl chloride (1.51g, 5.4mmol) was added. The reaction was stirred for 20 minutes, then allowed to warm to room temperature and stirred overnight. The reaction was then washed with ammonium chloride solution and the aqueous phase was back extracted three times with DCM. The combined organics were dried over Na_2SO_4, the solids were filtered off and the solvent evaporated. The crude product was then purified by flash chromatography (DCM eluent) to give the product after evaporation of the solvent and drying *in vacuo* as a colourless foam (2.02g, 95%).

Tlc (methanol - DCM, 1:9 v/v) R_f 0.74; $[\alpha]_D^{22}$ +79.6 (c 0.54, $CHCl_3$); IR (KBr Disc) ν_{max} 3419 (br); δ_H ($CDCl_3$) 0.63 (d, 3**H**, *J* 6.6), 2.14 (br. s, 1**H**), 2.69 (br. s, 1**H**), 2.94 (dq, 1**H**, *J* 3.1, 6.6), 3.85 (d, 1**H**, *J* 3.1), 7.05 (dd, 2**H**, *J* 1.2, 7.0), 7.12 (dd, 1**H**, *J* 5.5, 7.4), 7.18 (d, 1**H**, *J* 5.1), 7.19 (d, 2**H**, *J* 7.4), 7.20 (d, 2**H**, *J* 7.0), 7.28 (d, 3**H**, *J* 5.1), 7.29 (t, 1**H**, *J* 5.5), 7.30 (d, 3**H**, *J* 7.4), 7.58 (dd, 4**H**, *J* 1.2, 7.4), 7.59 (d, 2**H**, *J* 7.0); δ_C ($CDCl_3$) 15.64 (CH_3), 54.30, 71.89 (ipso), 74.78, 125.76, 126.85, 128.13, 128.19, 129.06, 142.35 (ipso), 146.79 (3 x ipso); HRMS (FAB) *m/z* 394.2180 [calcd for $C_{28}H_{28}NO$ (MH^+) 394.2171].

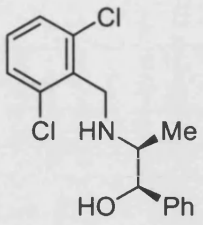
(1*R*,2*S*)-*N*-(2-Bromobenzyl)-2-amino-1-phenylpropan-1-ol (102)



(1*R*,2*S*)-Norephedrine (505mg, 3.3mmol) and $NaCNBH_3$ (210mg, 3.3mmol) were taken up in dry methanol (8ml). To this solution was added 2-bromobenzaldehyde (650mg, 3.5mmol). The reaction was carried out as for **98** above to give a colourless oil (**102**, 516mg, 48%).

Tlc (methanol - DCM, 1,9v/v) R_f 0.42; $[\alpha]_D^{23}$ -18.4 (c 1.63, $CHCl_3$); IR (thin film) ν_{max} 3400 (br); δ_H ($CDCl_3$) 0.86 (d, 3**H**, *J* 6.6), 2.68 (br. s, 2**H**), 2.95 (dq, 1**H**, *J* 3.9, 6.6), 3.93 (dd, 2**H**, *J* 3.5, 13.6), 4.80 (d, 1**H**, *J* 3.9), 7.14 (dt, 1**H**, *J* 1.7, 7.6), 7.23 (m, 1**H**), 7.28 (dd, 1**H**, 1.2, 7.4), 7.32 (m, 4**H**), 7.36 (dd, 1**H**, *J* 2.4, 7.4), 7.54 (dd, 1**H**, *J* 1.2, 7.8); δ_C ($CDCl_3$) 15.09 (CH_3), 51.64 (CH_2), 58.01, 73.39, 124.41 (ipso), 126.30, 127.31, 127.80, 128.32, 129.15, 130.70, 133.20, 138.97 (ipso), 141.38 (ipso); HRMS (FAB) *m/z* 320.0644 [calcd for $C_{16}H_{19}BrNO$ (MH^+) 320.0650].

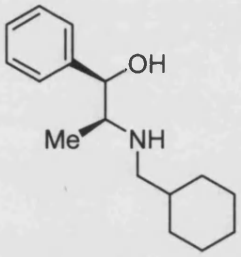
(1*R*,2*S*)-N-(2,6-dichlorobenzyl)-2-amino-1-phenyl propan-1-ol (103)



To a solution of (1*R*,2*S*)-norephedrine (805mg, 5.3mmol) in methanol (10ml) was added 2,6-dichlorobenzaldehyde (976mg, 5.57mmol). The solution was cooled to 0°C and to it was added $NaCNBH_3$ (343mg, 5.46mmol). After 10 minutes stirring the solution was allowed to warm to room temperature and was stirred for 4 days. The pH of the solution was maintained between 6-7 by periodic additions of 2M HCl. The reaction was then quenched with 2M HCl , and the products extracted using dichloromethane. The aqueous phase was washed a further two times with dichloromethane and the combined organics were dried over $MgSO_4$. The crude product was then purified by flash column chromatography (gradient elution; 100% DCM to 5% methanol-DCM) to give the product as a colourless powder (650mg, 39%). Tlc (methanol-DCM, 1:9 v/v) R_f 0.76; m.p. 75°C; $[\alpha]_D^{21}$ +26.2 (c 1.03, abs. ethanol); IR (KBr Disc) ν_{max} 3414 (br); δ_H ($CDCl_3$) 0.81 (d, 3**H**, *J* 6.2), 1.61 (br. s, 1**H**), 2.95 (dq, 1**H**, *J* 3.9, 6.6), 3.64 (br. s, 1**H**), 4.12 (d, 1**H**, *J* 12.9), 4.24 (d, 1**H**, *J* 12.9), 4.92 (d, 1**H**, *J* 3.9), 7.16 (dd, 1**H**, *J* 7.3, 8.8), 7.23 (m, 1**H**), 7.32 (m, 6**H**); δ_C ($CDCl_3$) 15.28 (CH_3), 46.37 (CH_2), 57.71, 72.79, 126.16, 127.13, 128.21, 128.63, 129.25, 135.65 (ipso), 136.11 (ipso), 141.29 (ipso); HRMS (FAB) *m/z* 310.0764 [calcd for $C_{16}H_{18}Cl_2NO$ (MH^+) 310.0766]. Anal.

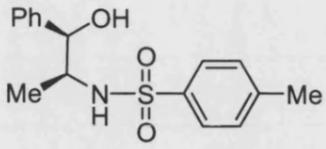
calcd for $C_{16}H_{17}Cl_2NO$: C, 61.95; H, 5.52; N, 4.52. Found C, 62.00; H, 5.55; N, 4.61.

(1*R*,2*S*)-*N*-(cyclohexylmethyl)-2-amino-1-phenyl propan-1-ol (104)



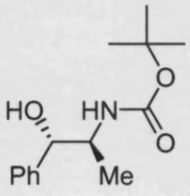
To a solution of (1*R*,2*S*)-norephedrine (805mg, 5.3mmol) in methanol (10ml) was added cyclohexane carboxaldehyde (603mg, 5.37mmol). The solution was cooled to 0°C and to the solution was added $NaCNBH_3$ (343mg, 5.46mmol). Using a procedure similar to **103**, the reaction afforded a colourless powder (860mg, 66%). Tlc (methanol - DCM, 2:8 v/v) R_f 0.37; m.p. 86°C; $[\alpha]_D^{19}$ +96.6 (c 1.04, EtOH); IR (KBr Disc) ν_{max} 3414 (br); δ_H ($CDCl_3$) 0.79 (d, 3**H**, *J* 6.2), 0.94 (m, 2**H**), 1.22 (m, 3**H**), 1.42 (m, 1**H**), 1.69 (m, 3**H**), 1.80 (dd, 1**H**, *J* 12.5, 1.6), 2.49 (dd, 1**H**, *J* 7.0, 11.3), 2.58 (dd, 1**H**, *J* 6.3, 11.3), 2.88 (dq, 1**H**, 3.9, 6.5), 4.74 (d, 1**H**, *J* 3.9), 7.29 (m, 5**H**); δ_C ($CDCl_3$) 15.27 (CH_3), 26.45 (CH_2), 26.48 (CH_2), 27.09 (CH_2), 31.84 (CH_2), 31.86 (CH_2), 38.77, 54.35 (CH_2), 58.83, 73.01, 126.23, 127.10, 128.21, 141.61 (ipso); HRMS (FAB) *m/z* 248.2010, [calcd for $C_{16}H_{26}NO$ (MH^+) 248.2014]; Anal. calcd for $C_{16}H_{25}NO$: C, 77.68; H, 10.19; N, 5.66. Found C, 77.80; H, 10.10; N, 5.81.

(1*R*,2*S*)-*N*-(4-toluenesulphonyl)-2-amino-1-phenyl propan-1-ol (105)



To a solution of (1*R*,2*S*)-norephedrine (1.34g, 8.8mmol) and *p*-toluene sulfonyl chloride (1.69g, 8.8mmol) in dichloromethane (10ml) was added triethylamine (1.48ml, 10.6mmol) and the reaction was stirred for 22 hours at room temperature. The reaction was then washed with water and extracted three times with DCM. The combined organics were dried over Na_2SO_4 and the remaining Et_3N was removed by azeotroping with ethanol. This afforded, after evaporation of the solvent, a colourless solid (2.79g, quant.). Tlc (methanol - DCM, 1:9 v/v) R_f 0.61; $[\alpha]_D^{26}$ -11.3 (c 1.24, $CHCl_3$); IR ($CDCl_3$) ν_{max} 3506, 3280; δ_H ($CDCl_3$) 0.83 (d, 3**H**, *J* 6.8), 2.42 (s, 3**H**), 2.52 (br. s, 1**H**, O<u>H</u>), 3.57 (br. s, 1**H**), 4.79 (d, 1**H**), 5.00 (br, d, 1**H**, *J* 8.2, N<u>H</u>), 7.28 (m, 7**H**), 7.78 (d, 2**H**, *J* 8.2); δ_C ($CDCl_3$) 14.64 (CH_3), 21.99 (CH_3), 55.51, 76.05, 126.29, 127.26, 127.68, 128.45, 129.99, 137.89 (ipso), 140.68 (ipso), 143.62 (ipso);

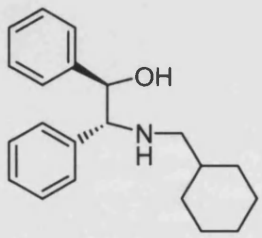
(1*R*,2*S*)-*N*-*tert*-Butyloxycarbonyl-2-amino-1-phenyl propan-1-ol (106)



To a solution of (1*R*,2*S*)-norephedrine (1.687g, 11.2mmol) in DCM (10ml) was slowly added di-*tert*-butyl dicarbonate (2.315g, 10.6mmol) and the reaction was allowed to stir for 2 hours until no more evolution of CO_2 could be seen. The reaction was then extracted with 1M $KHSO_4$ and the aqueous layer was washed twice with DCM. The combined organic layers were collected, dried over Na_2SO_4 and the solvent evaporated *in vacuo* to give colourless felted needles (2.195g, 82%). Tlc (methanol-DCM, 1:9 v/v) R_f 0.65; $[\alpha]_D^{26}$ -61.3 (c 1.01, $CHCl_3$); m.p. 91°C;

δ_H ($CDCl_3$) 0.98 (d, 3**H**, *J* 6.7), 1.46 (s, 9**H**), 3.01 (br. s, 1**H**), 3.99 (s, 1**H**), 4.70 (s, 1**H**), 4.84 (d, 1**H**, *J* 2.7), 7.27 (m, 1**H**), 7.34 (m, 4**H**); δ_C ($CDCl_3$) 15.17 (CH_3), 28.80 (CH_3), 52.37, 77.17, 80.08 (ipso), 126.51, 127.60, 128.31, 141.03 (ipso), 156.84 (ipso); HRMS (EI) *m/z* 251.1514, [calcd for $C_{14}H_{21}NO_3$ (M^+) 251.1521]; Anal. calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57. Found C, 66.70; H, 8.34; N, 5.48.

(1*R*,2*R*)-N-(cyclohexylmethyl)-2amino-1,2-diphenylethanol (111)

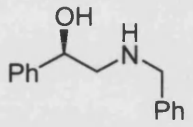


Cyclohexane carboxaldehyde (340mg, 3.0mmol) was taken up in methanol (10ml) and to the solution was added (1*R*,2*S*)-2-amino-1,2-diphenylethanol (587mg, 2.75mmol). The mixture was cooled to 0°C and $NaCNBH_3$ (182mg, 2.9mmol) was added. The reaction was stirred at 0°C for 45 mins with the pH of the solution being maintained at *ca.* pH6 by addition of 1M HCl. The reaction was then left to stir for two days at room temperature, then acidified with HCl solution to pH1-2. The methanol was evaporated and to the aqueous phase was added NaOH bringing the pH to 14. The aqueous suspension was then washed three times with DCM and the combined organic phases were dried over Na_2SO_4 and filtered. The crude product was purifed by flash column chromatography (gradient elution; DCM to MeOH - DCM (1:9 v/v)). A DCM solution of the product was washed with 1M HCl. The layers were separated, the aqueous phase back extracted 5 times with DCM and the combined organic phases were dried over Na_2SO_4 and filtered. The bulk of the solvent was evaporated and 5% NaOH solution was added. The layers were separated and the aqueous phase back extracted with DCM three times. The combined organic phases were once again dried over Na_2SO_4. The suspension was filtered and the solvent evaporated to give, after drying *in vacuo*, a colourless crystalline powder (353mg, 42%). Tlc (methanol - DCM, 1:9 v/v) R_f 0.44; m.p. 90°C; $[\alpha]_D^{21}$ +28.5 (c 1.0, $CHCl_3$);

δ_H ($CDCl_3$) 0.89 (m, 2**H**), 1.96 (m, 3**H**), 1.41 (m, 1**H**), 1.70 (m, 5**H**), 2.37 (dd, 1**H**, *J* 6.8, 11.8), 2.42 (dd, 1**H**, *J* 6.4, 11.5), 3.51 (d, 1**H**, *J* 8.6), 4.53 (d, 1**H**, *J* 8.6), 6.98 (d, 1**H**, *J* 5.5), 6.99 (d, 1**H**, *J* 5.9), 7.07 (d, 1**H**, *J* 5.9), 7.07 (d, 1**H**, *J* 7.4), 7.17 (m, 4**H**), 7.21 (m, 2**H**); δ_C ($CDCl_3$) 26.11

(CH_2), 26.13 (CH_2), 26.74 (CH_2), 31.35 (CH_2), 31.51, 38.35, 54.28 (CH_2), 70.86, 77.59, 126.72, 127.23, 127.47, 127.71, 128.12, 139.98 (ipso), 141.06 (ipso); HRMS (FAB) *m/z* 310.2171 [calcd for $C_{21}H_{28}NO$ (MH^+) 310.2171]; Anal. calcd for $C_{21}H_{27}NO$: C, 81.51; H, 8.79; N, 4.53. Found C, 80.90; H, 8.75; N, 4.73.

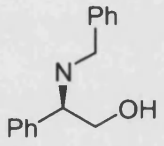
(1*R*)-*N*-Benzyl-2-amino-1-phenylethanol (112)



(*R*)-(+)-Styrene oxide (508mg, 4.23mmol) was taken up in anhydrous acetonitrile (3ml). To this solution was added benzylamine (2.27g, mmol) slowly over a period of five minutes. The mixture was then cooled to 0°C and to it was added a solution of 3M $LiClO_4$ in EtOAc (1.41ml, 4.23mmol) over 10 minutes. The reaction was stirred at 0°C for one hour and then allowed to warm to room temperature and stirred for a further 22 hours. The reaction was then cooled to 0°C and water (21ml) was added. The reaction was allowed to stir at this temperature for 40 mins and then the white precipitate was collected by suction filtration. The solid was washed with water and then dried overnight *in vacuo* to give a colourless crystalline power (**112**, 580mg, 60%) which was recrystallised from isopropanol to give colourless needles (460mg, 48%). $[\alpha]_D^{21}$ -56.1 (c 1.0, $CHCl_3$) Lit. $[\alpha]_D^{25}$ –54.6 (c 1.22, $CHCl_3$)[63]; IR (KBr Disc) ν_{max} 3142.7 (br); δ_H ($CDCl_3$) 2.29 (br. s, 2**H**), 2.75 (dd, 1**H**, *J* 9.0, 12.1), 2.94 (dd, 1**H**, 3.7, 12.3), 3.81 (d, 1**H**, *J* 13.3), 3.86 (d, 1**H**, *J* 13.3),

4.73 (dd, 1**H**, *J* 3.5, 9.0), 7.30 (m, 10**H**); δ_C ($CDCl_3$) 53.87 (CH_2), 54.85 (CH_2), 72.09, 126.01, 127.36, 127.71, 128.29, 128.57, 128.70, 140.03 (ipso), 142.57 (ipso); HRMS (FAB) *m/z* 228.1383 [calcd for $C_{15}H_{18}NO$ (MH^+) 228.1389]; Anal. calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found C, 79.10; H, 7.59; N, 6.35.

(*R*)-*N*-Benzyl-2-amino-2-phenylethanol (113)



To a refluxing solution of (*R*)-(-)-phenylglycinol (487mg, 3.55mmol) in dry methanol (4ml) over 3Å sieves was added over 40 minutes a solution of benzaldehyde (377mg, 3.55mmol) in methanol (2ml). The reaction was stirred at 80°C for 4 hours and, after cooling to room temperature, the solvent was evaporated. The crude product was taken up in DCM and dried over Na_2SO_4. The solids were filtered through a pad of Na_2SO_4 under suction and the solvent evaporated to leave a colourless oil. IR analysis showed it to be the desired imine. The oil was taken up in absolute ethanol (15ml) and the solution cooled to 0°C. Excess $NaBH_4$ (188mg, 4.97mmol) was added and the mixture was stirred at 0°C for 20 minutes after which time the reaction was complete by IR. To the reaction was then added water (0.5ml) and the mixture was stirred for a further 30 minutes. The solvent was then evaporated and the residue taken up in ethyl acetate. The organic layer was washed three times with water. The organic phase was dried over Na_2SO_4 and the solids filtered under suction.

Evaporation of the solvent and drying *in vacuo* resulted in a colourless solid. This was purified by flash column chromatography (gradient elution, 100% DCM to MeOH - DCM, 3:97 v/v) to give a colourless solid (507mg, 63%). The product was recrystallised from DCM - cyclohexane, 1:1 v/v, to give colourless needles.

Tlc (methanol-DCM, 1:9 v/v) R_f 0.54; $[a]_D^{22}$ -80.3 (c 0.66, abs. EtOH); IR (KBr) ν_{max} 3251, 3142 (br); δ_H ($CDCl_3$) 2.08 (br. s, 2**H**), 3.56 (dd, 1**H**, *J* 8.8, 10.7), 3.60 (d, 1**H**, *J* 12.5), 3.71 (dd, 1**H**, *J* 4.5, 10.7), 3.76 (d, 1**H**, 12.9), 3.82 (dd, 1**H**, 4.3, 8.6), 7.31 (m, 10**H**); δ_C ($CDCl_3$) 51.21 (CH_2), 63.75, 66.75 (CH_2), 126.97, 127.14, 127.57, 128.09, 128.32, 128.58, 139.90 (ipso), 140.33 (ipso); HRMS (FAB) *m/z* 228.1385 [calcd for $C_{15}H_{18}NO$ (MH^+) 228.1388].

6.7 GENERAL PROCEDURE FOR TRANSFER HYDROGENATION OF KETONES.

Procedure A

To a dry flask under argon was added [(*p*-cymene)$RuCl_2$]$_2$ (5 mol% [Ru]) and ligand (10 mol%). These were taken up in 2-propanol (ensuring final ketone concentration of 0.1M) and the solution was then heated at reflux for 1 hour. After this time, the dark red solution was allowed to cool to room temperature and KOH (0.5M solution in 2-propanol, 5 mol. eq. to [Ru]) was added. The mixture was stirred for a short time and the flask then placed in a bath at reaction temperature. To the solution was then added ketone (20 mol. eq. to Ru). The mixture was stirred for a given time and aliquots were removed for analysis. These aliqots were immediately quenched with diethyl ether and passed through a pad of silica to remove any metal.

Procedure B

To a dry flask under argon was added [(*p*-cymene)$RuCl_2$]$_2$ (5-6 mol% [Ru]) and ligand (5-6 mol%). These were taken up in 2-propanol (ensuring ketone concentration of 0.1M) and the solution was then heated at reflux for 1 hour. After this time, the dark red solution was allowed to cool to room temperature and KOH (0.5M solution in 2-propanol, 5 mol. eq. to [Ru]) was added. The mixture was stirred for a short time and the flask then placed in a bath at

reaction temperature. To the solution was then added ketone (20 mol. eq. to Ru). The mixture was stirred for a given time and aliquots were removed for analysis.

Procedure C

To a dry flask under argon was added [(*p*-cymene)$RuCl_2$]$_2$ (1 mol% [Ru]) and ligand (2 mol%). These were taken up in 2-propanol (ensuring ketone concentration of 0.1M) and the solution was then heated at reflux for 1 hour. After this time, the dark red solution was allowed to cool to room temperature and KOH (0.2M solution in 2-propanol, 5 mol. eq. to [Ru]) was added. The mixture was stirred for a short time and the flask then placed in a bath at reaction temperature. To the solution was then added ketone (100 mol. eq. to Ru). The mixture was stirred for a given time and aliquots were removed for analysis. These aliquots were immediately quenched with diethyl ether and passed through a pad of silica to remove any metal.

Product Analysis

Reactions were analysed by chiral HPLC, chiral GC and H-NMR.

<u>1-phenyl ethanol</u>

GC Column: β-Dex column; Column temperature: 115 °C; Carrier Pressure: 100 KPa; Retention times: ketone- 20.2 mins, (*R*) alcohol- 33.2mins, (*S*) alcohol 2- 36.1 mins.

HPLC Column: Chiralcel OD; Eluent: *n*-hexane - 2-propanol, 98:2 v/v; Flow rate: 1ml/min; Retention times: (*R*)-isomer - 12mins, (*S*)-isomer - 15mins

4-bromo-α-methylbenzyl alcohol

HPLC Column: Chiracel OD; Eluent: *n*-hexane- 2-propanol, 98:2 v/v; Flow rate: 1ml/min; Retention times: ketone - 6.9 mins, alcohol peaks 17.5 mins and 19.2 mins (absolute stereochemistry undetermined).

1-(2-napthyl)ethanol

HPLC Column: Chiracel OJ; Eluent: *n*-hexane- 2-propanol, 94:6 v/v; Flow rate: 1ml/min; Retention times: ketone - 10.9 mins, alcohol peaks - 13.9 mins and 17.1 mins (absolute stereochemistry undetermined).

4-methoxy-α-methylbenzylalcohol

GC Column: β-Dex column; Column temperature: 135 °C; Carrier Pressure: 200 KPa; Retention times: ketone- 28.1 mins, alcohol peaks - 31.3 mins and 32.8 mins (absolute stereochemistry undetermined).

HPLC Column: Chiracel OD column; Eluent: *n*-hexane- 2-propanol, 98:2 v/v; Flow rate: 1ml/min; Retention times: ketone - 10.5 mins, alcohol peaks - 21.8 mins and 25.2 mins (absolute stereochemistry undetermined).

1 Kagan, H.B.; Dang, T.; *J. Am. Chem. Soc.* **1972**, *94*, 6429.

2 Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R.; *J. Am. Chem. Soc.* **1980**, *102*, 7932.

3 Noyori, R.; Okuma, T.; Kitamura, M.; Takaya, H.; Sayo, N; Kumobayashi, H.; Akutagawa, S.; *J. Am. Chem. Soc.* **1987**, *109*, 5856.

4 Doucet, H.; Ohkuma, T.; Murata, K.; Yokozawa, T.; Kozawa, M.; Katayama, E.; England, A.; Ikariya, T.; Noyori, R.; *Angew. Chem. Int. Ed.*, **1998**, *37*, 1703.

5 Ojima, I.; Nihonyanagi, M.; Nagai, Y.; *J. Chem. Soc. Chem. Commun.*, **1972**, 938.

6 (a) Brunner, H.; Riepl, G.; *Angew. Chem. Int. Ed.*, **1982**, *21*, 377, (b) Brunner, H.; Reiter, B.; Riepl, G.; *Chem. Ber.*, **1984**, *117*, 1330.

7 (a) Brunner, H.; Becker, R. Riepl, G.; *Organometallics*, **1984**, *3*, 1354; (b) Brunner, H.; Kürzinger, A.; *J. Organometallic Chem.*, **1988**, *346*, 413.

8 Brunner, H.; Obermann, U.; Wimmer, P.; *J. Organometallic Chem.*, **1986**, *316*, C1.

9 Sudo, A; Yoshida, H.; Saigo, K.; *Tetrahedron: Asymmetry*, **1997**, *8*, 3205.

10 Lee, S.; Lim, C.; Song, C.; Kim, I.; *Tetrahedron: Asymmetry*, **1997**, *8*, 4027.

11 Nishibayashi, Y.; Takei, I.; Uemura, S.; Hadai, M.; *Organometallics*, **1998**, *17*, 3420.

12 Bianchi, M.; Matteoli, U.; Menchi, G.; Frediani, P.; Pratesi, S.; Piacenti, F.; *J. Organometallic Chemistry*, **1980**, *198*, 73.

13 Krause, H.W.; Bhatnagar, A.K.; *J. Organometallic Chem.*, **1986**, *302*, 265.

14 Barbaro, P.; Bianchini, C.; Togni, A.; *Organometallics*, **1997**, *16*, 3004.

15 Sammakia, T.; Stangeland, E.L.; *J. Org. Chem.*, **1997**, *62*, 6104.

16 Jiang, Q., Plew, D.V.; Murtuza, S.; Zhang, X.; *Tetrahedron Letters*, **1996**, *37*, 797.

17 Jiang, Y., Jiang, Q.; Zhu, G.; Zhang, X.; *Tetrahedron Letters*, **1997**, *38*, 215.

18 Jiang, Y., Jiang, Q.; Zhang, X.; *J. Am. Chem. Soc.*, **1998**, *120*, 3817.

19 Gamez, P.; Fache, F.; Mangeney, P.; Lemaire, M.; *Tetrahedron Lett.*, **1993**, *43*, 6897.

20 Gamez, P.; Fache, F; Lemaire, M.; *Tetrahedron Asymmetry*, **1995**, *6*, 705.

21 Hashiguchi, S.; Fujii, A.; Takehara, J.; Ikariya, T.; Noyori, R.; *J. Am. Chem. Soc.*, **1995**, *117*, 7562.

22 Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R.; *J. Am. Chem. Soc.*, **1996**, *118*, 2521.

23 Püntener, K.; Schwink, L.; Knochel, P.; *Tetrahedron Lett.*, **1996**, *37*, 8165.

24 (a) Touchard, F.; Gamez, P.; Fache, F.; Lemaire, M.; *Tetrahedron Lett.*, **1997**, *38*, 2275. (b) Touchard, F.; Fache, F.; Lemaire, M.; *Tetrahedron: Asymmetry*, **1997**, *8*, 3319.

25 Takehara, J.; Hashiguchi, S.; Fujii, A.; Inoue, S.; Ikariya, T.; Noyori, R.; *J. Chem. Soc., Chem. Commun.*, **1996**, 233.

26 Palmer, M.; Walsgrove, T.; Wills, M.; *J. Org. Chem.*, **1997**, *62*, 5226.

27 Alonso, D.; Guijarro, D.; Pinho, P.; Temme, O.; Andersson P.; *J. Org. Chem.*, **1998**, *63*, 2749.

28 Halle, R.; Bréhéret, A.; Schulz, E.; Pinel, C.; Lemaire, M.; *Tetrahedron: Asymmetry*, **1997**, *8*, 2101.

29 Yamakawa, M.; Hisashi, I.; Noyori, R.; *J. Am. Chem. Soc.*, **2000**, *122*, 1466.

30 Haack, K.; Hashiguchi, S.; Fujii, A.; Ikariya, T.; Noyori, R.; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 285.

31 Noyori, R.; Hashiguchi, S.; *Acc. Chem. Res.*, **1997**, *30*, 97.

32 Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R.; *J. Am. Chem. Soc.* **1996**, *118*, 2521.

33 (a) Wolfe, J.P.; Wagaw, S.; Buchwald, S.L.; *J.Am.Chem. Soc* **1996**, *118*, 7215; (b) Driver, M.S.; Hartwig, J.F.; *J. Am Chem. Soc.* **1996**, *118*, 7217.

34 Beletskaya, I.P.; Bessmertnykh, A.G.; Guilard, R. *Tetrahedron Lett.* **1997**, *38*, 2287.

35 Frost, C.G.; Mendonça, P.; *Chemistry Letters*, **1997**, 1159.

36 (a)Wolfe, J.P.; Tomori, H.; Sadighi, J.P.; Yin, J.; Buchwald, S.L.; *J. Org. Chem.* **2000**, *65*, 1158; (b) Marcoux, J.F.; Wagaw, S.; Buchwald, S.L; *J. Org. Chem.* **1997**, *62*, 1568; (c) Vyskočil, S.; Smrčina, M.; Kočovský, P.; *Tetrahedron Lett.* **1998**, *39*, 9289.

37 Wolfe, J.P.; Buchwald, S.L.; *J. Org. Chem.* **1996**, *61*, 1113.

38 Wagaw, S.; Rennels, R.A.; Buchwald, S.L.; *J. Am. Chem. Soc.* **1997**, *119*, 8451.

39 Rossen, K.; Pye, J.P.; Maliakal, A.; Volante, R.P.; *J. Org. Chem.* **1997**, *62*, 6462.

40 Wolfe, J.P.; Buchwald, S.L.; *J. Org. Chem.*, **1997**, *62*, 6066.

41 Draper, T.L.; Bailey, T.R.; *Synlett*, **1995**, *2*, 157.

42 Corey, E.J.; Imwinkelried, R.; Pikul, S.; Xiang, Y.B.; *J. Am. Chem. Soc.* **1989**, *111*, 5493.

43 Wagaw, S.; Rennels, R.A.; Buchwald, S.L.; *J. Am. Chem. Soc.* **1997**, *119*, 8451.

44 Fujii, A.; Hashiguchi S.; Uematsu N.; Ikariya T.; Noyori R.; *J. Am. Chem. Soc.* **1996**, *118*, 2521.

45 Sadighi, J.P.; Harris, M.C.; Buchwald, S.L.; *Tetrahedron Letters*, **1998**, *39*, 5327.

46 Evans, D.A.; Nelson, S.G.; Gagné, M.R.; Muci, A.R.; *J. Am. Chem. Soc.*, **1993**, *115*, 9800.

47 Zassinovich, G; Bettella, R.; Mestroni, G.; Bresciani-Pahor, N.; Geremia, S.; Randaccio, L.; *J. Organometallic Chemistry*, **1989**, *370*, 187.

48 Gladiali, S.; Pinna, L.; Delogu, G.; De Martin, S.; Zassinovich, G; Mestroni, G.; *Tetrahedron: Asymmetry* **1990**, *1*, 635.

49 Müller, D.; Umbricht, G.; Weber, B.; Pfaltz, A.; *Helvetica Chimica Acta*, **1991**, *74*, 232.

50 (a) Noyori, R.; Hashiguchi, S.; *Acc. Chem. Res.*, **1997**, *30*, 97. (b) Gao, J.; Ikariya, T.; Noyori, R.; *Organometallics*, **1996**, *15*, 1087.

51 Langer, T.; Helmchen, G.; *Tetrahedron Lett.*, **1996**, *37*, 1381.

52 Arikawa, Y.; Ueoka, M.; Matoba, K.; Nishibayashi, Y.; Hidai, M.; Uemura, S.; *J. Organometallic Chem.*, **1999**, *572*, 163.

53 Jiang, Y.; Jiang, Q.; Zhu, G.; Zhang, X.; *Tetrahedron Lett.*, **1997**, *38*, 215.

54 Takehara, J.; Hashiguchi, S.; Fujii, A.; Inoue, S.; Ikariya, T.; Noyori, R.; *J. Chem. Soc., Chem. Commun.* **1996**, 233.

55 Inoue, S.; Nomura, K.; Hashiguchi, S.; Noyori, R.; Izawa, Y.; *Chemistry Letters*, **1997**, 957.

56 Bernard, M.; Guiral, V.; Delbecq, F.; Fache, F.; Sautet, P.; Lemaire, M.; *J. Am. Chem. Soc.*, **1998**, *120*, 1441.

57 (a) Noyori, R.; Hashiguchi, S.; *Acc. Chem. Res.* **1997**, *30*, 97. (b) Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R.; *J. Am. Chem. Soc.* **1996**, *118*, 4916. (c) Wang, G.; Bäckvall, J.; *J. Chem. Soc., Chem. Commun.* **1992**, 980.

58 Yamakawa, M.; Hisashi, I.; Noyori R.; *J. Am. Chem. Soc.* **2000**, *122*, 1466.

59 Alonso, D.A.; Brandt, P.; Nordin, S.J.M.; Andersson, P.G.; *J. Am. Chem. Soc.* **1999**, *121*, 9580.

60 Ruthenium loading of 5 mol. %.

61 (a) Fodor, G.; Bruckner, V.; Kiss, J.; Ohegy, G.; *J. Org. Chem.* **1949**, *14*, 337. (b) Grunewald, G.L.; Ye, Q.; *J. Med. Chem.* **1988**, *31*, 1984.

62 Weijlard, J.; Pfister, K.; Swanezy, E.F.; Robinson, C.A.; Tishler, M.; *J. Am. Chem. Soc.* **1951**, *73*, 1216.

63 Remuzon, P.; Soumeillant, M.; Dussy, C.; Bouzard, D.; *Tetrahedron*, **1997**, *53*, 17711.